

TREATMENT ADHERENCE: REPORTING GUIDELINES AND THE SHOWCASE OF HEART TRANSPLANTATION (PREVALENCE & PRACTICE PATTERNS)

Inaugural dissertation

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*To my parents... and to everyone who helped me cross obstacles and
lighted my road whenever it was dark*

Table of Contents

	Acknowledgments	I
	List of abbreviations	IV
	Summary	1
Chapter 1	Introduction	10
Chapter 2	Research aims	30
Chapter 3	ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): A reactive-Delphi study protocol	34
Chapter 4	ESPACOMP Medication Adherence Reporting Guideline (EMERGE)	52
Chapter 5	Higher prevalence of medication non-adherence to co-medications than to immunosuppressants in heart transplant recipients: findings from the international cross-sectional BRIGHT study	72
Chapter 6	Practice patterns to improve pre- and post-transplant medication adherence in heart transplant centres: A secondary data analysis of the international BRIGHT study	86
Chapter 7	The international prevalence and variability of nonadherence to the nonpharmacologic treatment regimen after heart transplantation: findings from the cross-sectional BRIGHT study	110
Chapter 8	Synthesis and discussion	136
	Curriculum vitae	158

Acknowledgements

As I grew up, I became more and more convinced that learning does not have to be limited to certain places or curricula. Hence, observing and analyzing data and using the results to make decisions have become an intrinsic part of my everyday life. These data span a wide spectrum from daily life situations that involve mainly myself, to research-based data that involve many other people. Through this learning process, I came to a, hopefully, better and clearer understanding of how the world functions. More importantly, I became aware of the fact that understanding one's self is equally important and as life progresses, this understanding of the self and the world needs to be continuously updated. Indeed, a Bayesian approach to understanding the world is appropriate where this understanding is updated as more data become available.

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Remon Helmy

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“Drugs don’t work in patients who don’t take them.”

Charles Everett Koop, MD, US Surgeon General, 1985

List of abbreviations

Abbreviation	Meaning
BAASIS	Basel Assessment of Adherence to Immunosuppressive Medications Scale
BMI	Body Mass Index
BRIGHT	Building Research Initiative Group: chronic illness management and adHerence in Transplantation
CFIR	Consolidated Framework for Implementation Research
CI	Confidence Interval
CIM	Chronic Illness Management
CO	Carbon Monoxide
CONSORT	CONsolidated Standards Of Reporting Trials
CVD	Cardiovascular Diseases
EMERGE	ESPACOMP Medication Adherence Reporting GuidelinE
EQUATOR	Enhancing the QUALity and Transparency Of health Research
ESPACOMP	The European Society for Patient Adherence, COMpliance, and Persistence
GDP	Gross Domestic Product
IMBP	Integrative Model of Behavioral Prediction
IQR	Interquartile Range
IS	Immunosuppressant(s)/Immunosuppression/Immunosuppressive
ISHLT	The International Society for Heart and Lung Transplantation
HTx	Heart Transplant(ation)
KTx	Kidney Transplantation
MNA	Medication Non-Adherence
OR	Odds Ratio
p	P-Value
StaRI	Standards for Reporting Implementation Studies
SD	Standard Deviation
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TIDieR	Template for Intervention Description and Replication
Tx	Transplant(ation)
UK	United Kingdom
US/USA	United States of America

Summary

Chronic conditions have become the global epidemic of the 20th and 21st century (1). Chronically ill patients follow a lifelong treatment of pharmacologic and non-pharmacologic components, which represents a huge burden (2) and leads to non-adherence (3). An awareness of the extent of the treatment non-adherence problem and its consequences on the individual and societal levels has led to dedicated efforts to research the problem in an attempt to remedy it. This dissertation deals with this topic and was conducted as a sub-project embedded in its two main constituting projects, ESPACOMP (the European Society for Patient Adherence, COMpliance, and Persistence) Medication Adherence Reporting Guideline (**EMERGE**) and Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (**BRIGHT**).

EMERGE is an initiative led by members and founding members of ESPACOMP (the European Society for Patient Adherence, Compliance, and Persistence). Its aim was to develop a guideline for reporting medication adherence research. The development of the guideline followed a structured process and incorporated input from topic experts worldwide. More details on EMERGE can be found in its published protocol, which is also the third chapter of this dissertation (4).

BRIGHT is an international cross-sectional study of 1397 heart transplant (HTx) recipients, 100 clinicians and directors of 36 HTx centers in 11 countries on four continents. The main aims of the primary study were:

1. To describe chronic illness management (CIM) practice patterns in centers, countries/continents in HTx
2. To assess the prevalence and variability of non-adherence to treatment regimen, i.e. medication-taking, cessation of smoking, diet adherence, alcohol consumption, physical activity, sun protection and appointment keeping in HTx recipients in centers, countries/continents
3. To determine which multi-level factors are related to immunosuppressive medication adherence
4. To benchmark participating centers, countries and continents in relation to CIM practice patterns and non-adherence to health behaviors.

More details on BRIGHT can be found in its published protocol (5).

This dissertation is organized into **8 chapters** as follows: **chapter 1** introduces the treatment adherence topic and the knowledge gaps that are covered in the dissertation. It starts

by highlighting the treatment burden of chronically ill patients and, subsequently, how the problem of non-adherence arises. It moves on to clarify the consequences of non-adherence and its global burden in light of the increasing prevalence of chronic conditions worldwide. It then focuses on HTx recipients and their lifelong need to follow a complex treatment regimen of immunosuppressants (IS), other medications, lifestyle changes and follow-up care as an interesting subpopulation of chronically ill patients in which to investigate treatment adherence. In addition, the chapter introduces health behavior theories and briefly discusses the two models used in designing the BRIGHT study, namely the integrative model of behavioral prediction and the ecological model for medication adherence. A medication adherence taxonomy (6) that represents the core of EMERGE is then introduced. The taxonomy disentangles the medication adherence concept into three constituting phases: initiation, implementation and persistence. The chapter ends with an explanation of the knowledge gaps that the dissertation deals with and the rationale behind filling them.

Based on these research gaps, **chapter 2** summarizes the aims of the dissertation which are:

1. To develop guidelines for reporting medication adherence research
2. To assess and compare the prevalence of medication non-adherence (MNA) (implementation and persistence phases) to immunosuppressants and co-medications in HTx recipients
3. To describe the international practice patterns with regard to medication adherence assessment methods and intervention strategies across the transplantation continuum at HTx centers
4. To assess the international prevalence and variability in non-adherence to six components of the post-HTx non-pharmacologic treatment (physical activity, sun protection, diet, alcohol use, non-smoking and outpatient follow-up visits)

Chapters 3-7 present the studies fulfilling these aims as a part of the EMERGE and BRIGHT studies as follows:

Chapters 3 and 4 of the dissertation represent EMERGE and focus on developing a guideline for reporting medication (pharmacologic treatment) adherence research. Given the observed inconsistency in reporting medication adherence research (7-9), a steering committee of members of ESPACOMP took the initiative to develop EMERGE as a way of normalizing the use of the abovementioned taxonomy in reporting such research. EMERGE was developed through a structured process following the guidance for developers of health research reporting guidelines (10). The EMERGE steering committee started the process by generating a pool of items that were used to formulate an initial item list. An international

group of medication adherence experts was then asked for their opinion on the initial list in two rounds of a Delphi study (11), the protocol of which is described in **chapter 3**. Based on pre-defined decision rules, the initial items could be deleted or modified, or new items could be suggested. The item list resulting from the Delphi study was approved after further fine-tuning by ESPACOMP members during the ESPACOMP annual meeting in 2016 in Lisbon, Portugal.

Chapter 4 presents the final guideline and explains the rationale behind the items on the final list. The final EMERGE item list is composed of two sections. The first section contains four items that represent minimum reporting criteria (medication adherence phase, operational definition, measurement, results) for medication adherence research. The second section consists of 17 items organized according to the sections of the most commonly used health research reporting guidelines (i.e. CONSolidated Standards Of Reporting Trials (CONSORT) (12), STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (13)) and avoids redundancy with them. EMERGE emphasizes the importance of reporting the phase(s) of medication adherence studied (initiation, implementation, or persistence). In this regard, it asks authors of medication adherence research articles to review literature, formulate research aims, use research methodology and report and discuss results appropriately for each medication adherence phase studied. In this way, consistency in reporting medication adherence research can be ensured, which in turn makes the reported research results more useful.

Moving on to the HTx patient population, **chapters 5-7** of the dissertation use data from the international BRIGHT study and focus on treatment adherence in HTx recipients as a subpopulation of chronically ill patients with a lifelong need for a complex treatment regimen and professional follow-up.

First, the dissertation investigates the prevalence of non-adherence to all post-HTx medications. Given that all post-HTx medications (immunosuppressants and co-medications) are vital to good transplant outcomes (14-18), it is imperative that HTx recipients adhere to their prescribed medication. **Chapter 5** describes and compares the prevalence of non-adherence to both categories of medication in detail, focusing on the implementation and persistence phases and the corresponding dimensions (for the implementation phase: taking, drug holiday, timing and dose alteration). Using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS®) (19), medication non-adherence (MNA) was assessed through self-report in an interview with HTx recipients during their outpatient clinic follow-up visit. BAASIS consists of five items: four dealing with implementation dimensions with a recall period of four weeks and one on persistence with a recall period of

one year. For co-medications, the timing dimension was omitted as it is not always important to take all other medications within two hours of the prescribed time.

Implementation MNA of IS was observed in 37.4% of the sample. More specifically, the prevalence of IS MNA was 17.3% for taking, 1.9% for drug holiday, 28.7% for timing and 1.6% for dose alteration. In view of discontinuation (non-persistence), we found a prevalence of 0.5%. The prevalence of MNA to co-medications was: 23.9% for taking, 5.7% for drug holiday, 28.7% for timing, 3.8% for dose alteration and 2.6% for discontinuation. Significantly higher levels of MNA to IS compared to MNA to co-medications was found in all the comparison dimensions: taking (OR=1.50; 95%CI=1.30-1.73, $p<0.0001$), drug holiday (OR=3.17; 95%CI=2.13-4.73, $p<0.0001$), dose alteration (OR=2.46; 95%CI=1.49-4.06, $p=0.0004$) and discontinuation (OR=5.15; 95%CI=2.36-11.20, $p<0.0001$). These results point to the need for adherence-enhancing interventions for all post-HTx medications, and further assessment of the underlying mechanisms of the higher non-adherence to co-medications.

The dissertation continues to discuss medication adherence in HTx recipients and in **chapter 6** describes the process of management of adherence (practice patterns) (6) by HTx center clinicians internationally along the HTx continuum. On a 27-item questionnaire, 100 clinicians from the 36 HTx centers (one to five per center) reported their practice patterns with regard to medication adherence assessment and intervention strategies at the following four time points: pre-transplant, immediately post-transplant, less than one year and one or more years post-transplant. Educational/cognitive, counselling/behavioral and psychosocial/affective intervention strategies were assessed. Clinicians' responses (intervention present vs. absent; or incongruence in reporting intervention) were aggregated at the center level.

Questioning patients (self-report) was the most commonly used adherence assessment method along the transplant continuum (75-88.9% of the centers). Pre-transplant, providing reading materials (82.9%) or instructions (68.6%), involving family or support persons in education (91.4%) and establishing partnerships (91.4%) were used most frequently. Training patients (during recovery) and cueing were more often applied during hospitalization (74.3%). After the first year post-transplant, except for motivational interviewing (25.7-28.6%), the number of adherence-enhancing strategies decreased. Given the observed decrease in medication adherence over time post-HTx (20) and the relatively stagnant long-term prognosis (21, 22), increased investment in long-term medication adherence-enhancing interventions is necessary.

Besides medication, HTx recipients are usually recommended to make certain lifestyle changes and to attend regular follow-up appointments at an outpatient clinic. It is equally

important that they adhere to this non-pharmacologic treatment regimen (23). **Chapter 7** investigates the prevalence and between-country variability of non-adherence to this treatment regimen in HTx recipients using self-report. The non-adherence definitions used were: physical activity: <3 times/week 20 minutes' vigorous activity, <5 times/week 30 minutes' moderate activity, or <5 times/week a combination of either intensity; sun protection: not "always" applying any sun protection; diet: not "often" or "always" following recommended diet(s); alcohol use: > 1 alcoholic drink/day (women) or > 2 drinks/day (men); smoking: current smoker or stopped <1 year before; follow-up visits: missing ≥ 1 of the last 5 outpatient follow-up visits. Between-country variability was assessed within each treatment component via chi-square testing.

The adjusted study-wide non-adherence prevalence figures were: 47.8% for physical activity (95% CI [45.2-50.5%]), 39.9% for sun protection (95% CI [37.3-42.5%]), 38.2% for diet recommendations (95% CI [35.1-41.3%]), 22.9% for alcohol consumption (95% CI [20.8%-25.1%]), 7.4% for cessation of smoking (95% CI [6.1%-8.7%]) and 5.7% for follow-up visits (95% CI [4.6-6.9%]). Moreover, significant variability was observed between countries in all treatment components except follow-up visits. These findings suggest a need for setting-tailored adherence-enhancing interventions for the non-pharmacologic treatment.

Chapter 8 of this dissertation summarizes these key findings and discusses them, including some reflections. These findings are: 1) developing EMERGE (European Society for Patient Adherence, COMpliance, and Persistence Medication Adherence Reporting Guideline), 2) non-adherence to the post-HTx medication was prevalent in all of the investigated phases and dimensions and was significantly higher in co-medications than in immunosuppressants, 3) regarding pre- and post-HTx adherence management practice patterns, questioning patients was the most commonly used adherence assessment method and the frequency of using almost all adherence interventions decreased post-HTx, and 4) non-adherence to the post-HTx non-pharmacologic treatment occurred in all the investigated health behaviors, in almost all country-behavior combinations, more frequently in some behaviors than in others, and more frequently in some countries than in others.

The chapter concludes by stating that non-adherence to pharmacologic and non-pharmacologic treatments remains a challenge that the healthcare system and all its stakeholders face. Having covered knowledge gaps on the levels of patients, clinicians, policy/decision-makers and researchers, this dissertation contributes to the ultimate goal of better treatment adherence and outcomes. Sound reporting of medication adherence research using EMERGE will increase the utility of the research results. At the same time, equipping clinicians with adequate measures of adherence could lead to better description of HTx-recipients' adherence behavior and the identification of those with inadequate adherence.

Accordingly, targeting all components of the post-HTx treatment regimen where non-adherence occurs using tailored multicomponent adherence-enhancing interventions would be possible along the HTx continuum and should lead to better treatment adherence and outcomes.

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Chapter

1

Introduction

Introduction

1.1 Treatment adherence in chronic conditions and its consequences

Patients living with chronic conditions, those lasting three months or longer (1), face the challenge of having to follow complex long-term therapies. These usually consist of medication (pharmacologic treatment), and lifestyle changes and follow-up with professional caregivers (collectively referred to as non-pharmacologic treatment). Beyond this, as the condition becomes an intrinsic part of their everyday life, they need to observe their conditions continuously (2) (self-monitoring) (e.g. monitoring blood glucose levels in the case of diabetic patients) and make informed decisions to manage them (2) (self-management) (e.g. adjusting their blood glucose level by administering an appropriate dose of their recommended treatment). **Hence, living with one or more chronic conditions represents a tremendous burden for chronically ill patients and the issue of treatment non-adherence arises.**

Adherence to long-term therapies, defined as the extent to which a person's behavior corresponds with agreed recommendations from a health care provider (3), is essential for achieving better outcomes on individual and societal levels. However, the problem of treatment non-adherence is widespread. A meta-analysis of 520 studies on non-adherence to treatment regimens (4) prescribed by a non-psychiatrist physician, reported an average non-adherence prevalence of 20.6% for medications, 28% for exercise, 30.3% for health behaviors, 34.1% for appointment keeping and 60.7% for diet. **Poor adherence or non-adherence is associated with worse patient outcomes** (e.g. slower or no improvement in the treated condition, preventable emergency department visits, hospitalizations, mortality) **and, correspondingly, worse societal outcomes** (e.g. higher disease burden, lower productivity, increased healthcare utilization) (5-8). For example, a meta-analysis of 44 studies on cardiovascular diseases (CVD) attributed 9.1% of CVD events in Europe to poor adherence to CVD medication (9). In the same way, lower adherence to lipid-lowering drugs was associated with worse prognosis, survival and quality of life (10). In heart transplantation (HTx), non-adherence to immunosuppressants was associated with higher incidence of transplant coronary artery disease (11). Although less investigated than medication non-adherence (MNA), non-pharmacologic treatment non-adherence has similarly detrimental consequences. Non-adherence to a sodium-restricted diet, for example, was found to be associated with greater symptom burden and shorter cardiac event-free survival in patients with heart failure (12). Similarly, non-adherence to follow-up visit appointments was a

significant risk factor for kidney graft loss (13) and late acute cardiac graft rejection episodes (14) in transplant recipients.

A recent systematic review of 79 studies (15) investigated the annual costs caused by medication non-adherence, including pharmacy, inpatient, outpatient, emergency department visit, medical and hospitalization costs. It found that the total annual cost of medication non-adherence per person across all disease groups ranged from \$949 to \$52,341, adjusted to the 2015 US\$ value to allow for a comparison between studies. On the country level, the annual cost of medication non-adherence was estimated to be \$100 billion in the US (16). Similar studies on the cost of non-pharmacologic treatment non-adherence are lacking.

1.2 Chronic conditions in the 20th and 21st centuries

This burden of non-adherence consequences is aggravating due to the increasing prevalence of chronic conditions. Owing to technological advancements, chronic conditions have become the global epidemic of the late modern era. Advances in treating communicable (infectious) diseases have led to better survival and life expectancy (17). As a result, the proportion of older people in the population has been steadily increasing since the 20th century (18). At the same time, recent technological developments have commonly been accompanied with more risk factors for chronic conditions. For instance, an estimate of 45% of all deaths in the USA in 2000 were attributed to personal decisions (the majority of which were decisions related to risk factors for chronic conditions, e.g. smoking, having an unhealthy diet, insufficient physical activity, alcohol consumption), in contrast to only 5% in 1900 (19). **The shift in the world's population pyramid has led to prolonged exposure and technological advancements have led to more opportunities of exposure to risk factors of chronic conditions. Combined, these factors have led to a higher incidence of chronic conditions.** On the other hand, advances in controlling, not curing, chronic conditions have led to rising numbers of people surviving with these conditions (**higher prevalence**). Indeed, the prevalence of chronic conditions has been rising worldwide in an unprecedented fashion since the 20th century. In the US, for example, an estimated 50% of all adults had at least one chronic condition in 2012 (20). Worldwide, 22% of adults 18 years or older had hypertension and 9% had diabetes in 2014 (21). Thus, problems related to chronically ill patients (including treatment non-adherence) represent a major challenge to the current healthcare system.

1.2.1 Heart transplantation as a chronic condition

One subpopulation of chronically ill patients is heart transplant (HTx) recipients. HTx as a treatment option for patients with end-stage heart disease has become more successful in terms of graft and recipient survival as a result of advancements in surgical techniques, immunosuppression and infection control (22). Based on this improvement in outcomes, the demand for HTx has been increasing. According to the Global Observatory on Donation and Transplantation (23), the number of heart transplants performed globally (107 countries) rose from 2,259 in 2000 to 7,012 in 2015. Consequently, HTx recipients represent an interesting and increasing patient population. HTx, though, is more a life-sparing treatment than a complete cure. Indeed, by receiving a transplant, patients gain improvement in their cardiac and consequently physiological and physical functions but remain reliant on a lifelong treatment regimen, professional healthcare and self-monitoring and -management. **In other words, by receiving the cardiac transplant, HTx recipients move from one illness state (end-stage heart disease) to another less severe but chronic state (post-HTx).**

Undeniably, HTx recipients, as chronically ill patients, require lifelong adherence to a regimen of immunosuppressants (24). One problem with immunosuppressants, however, is that they are associated with several side effects and might lead to other chronic conditions. More specifically, common comorbidities attributed to immunosuppressants intake at 5 years following HTx include renal dysfunction (51.1%), diabetes (35.5%) and malignancy (15.9% all types combined; skin malignancy has the highest prevalence at 9.5%) (25). Furthermore, HTx recipients might have other chronic conditions pre-HTx that continue to post-HTx. As a result, recipients' post-HTx treatment regimen typically includes other long-term medication and the lifelong adoption of a non-pharmacologic treatment regimen (24) to avoid, or at least delay, the incidence or progression of other comorbidities and to ensure favorable outcomes. This non-pharmacologic treatment regimen includes being physically active, not smoking, limiting alcohol intake, applying sun protection, following certain dietary recommendations (e.g. a low-salt or low-fat diet) and infection control (24). Furthermore, HTx recipients need to be regularly followed up by specialized healthcare professionals to monitor their condition, check them for any sign of cardiac graft rejection, train them in self-management and follow up on and adjust their treatment plans (24). In addition, as chronically ill patients, they need to monitor their condition continuously and make informed decisions to adjust their treatment accordingly.

For these reasons, HTx recipients represent a particularly susceptible population of chronically ill patients who follow a complex therapeutic regimen and who are likely to become non-adherent (26) to any of their treatment

components. Given the importance of this treatment regimen to the survival of HTx recipients and their cardiac grafts, and given the scarcity of the cardiac grafts available compared to the number of patients on transplantation waiting lists (27), adherence to the treatment regimen is critical (11, 28). Worth introducing in this regard is BRIGHT (Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation), a cross-sectional study of 1397 HTx recipients, 100 clinicians and directors from 36 HTx centers in 11 countries and four continents. Assuming that treatment non-adherence is multifactorial, this study investigated the prevalence and multi-level correlates of treatment non-adherence. This dissertation uses data from BRIGHT to achieve some of its aims. Hereinafter, theories and models constructed to explain treatment (health behaviors) adherence will be introduced briefly while highlighting the two models used to design the BRIGHT study. After that, the two major treatment components (pharmacologic and non-pharmacologic) will be dealt with separately while highlighting knowledge gaps in each component. Adult HTx recipients will be focused on as a population of interest with the goal of describing the processes of adherence to treatment and management of adherence (29) in this patient population to determine possible system leverage points as a step towards enhancing their outcomes.

1.3 Health behavior theories and ecological models

Several health behavior theories have been proposed as an explanation of how patients enact health behaviors or follow prescribed treatments (30). Examples of such theories include the theory of planned behavior (31), the social cognitive theory (32), the health belief model (33) and the integrative model of behavioral prediction (IMBP) (34). While these theories have often been criticized (35, 36), they could provide foundations for conceptualizing human health behavior dynamics. For instance, the IMBP, a model of health behaviors that integrates many factors from other models, depicted in **figure 1.1**, posits that the most proximal determinant of a person's behavior is intention. In this model, this cause-effect relationship between intention and behavior is moderated by a person's skills and abilities and other environmental factors. IMBP proposes that an individual's attitudes, norms and self-efficacy are, in turn, determinants of intention and affected by a multitude of other variables including a person's demographic and cultural variables.

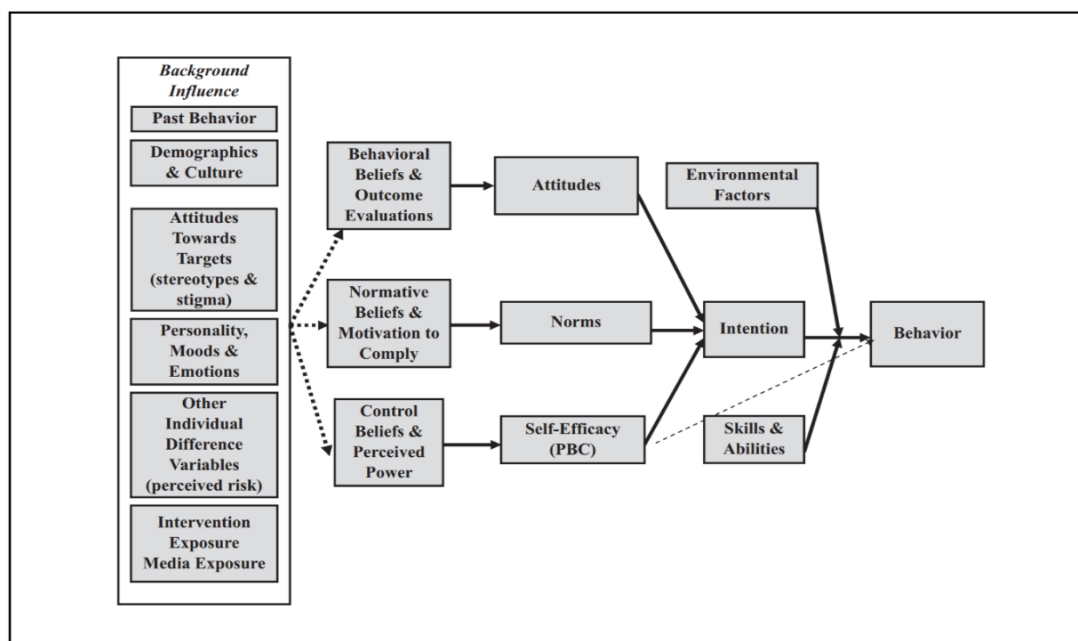
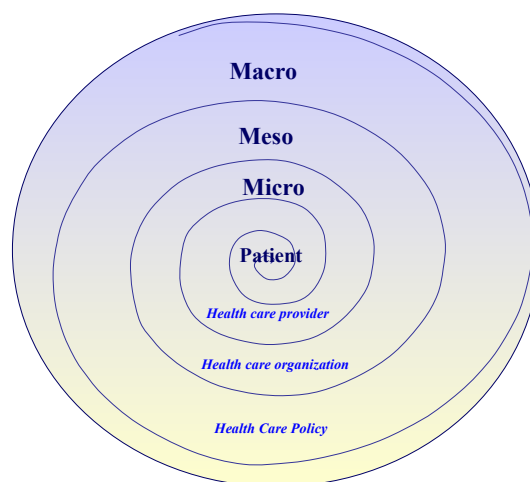


Figure 1.1: The Integrative Model of Behavioral Prediction

These theories, however, are partial in their views of human health behaviors. They focus mostly on patients, and rarely consider factors beyond as affecting patients' health behaviors (31-33, 37, 38). In fact, although these theories consider external factors, their focus tends to be on patients' perceptions of the factors or the patients' ability to enact the behavior in the presence/absence of the factors, rather than on the direct effects of these factors on behavior. In other words, most of the health behavior theories have focused predominantly on the psychological dynamics of the individual's health behavior. A more holistic view of health behavior and its determinants would be more suitable since patients, as individual actors, do not behave in a vacuum but rather in a multi-level environment that influences their actions.

Figure 1.2 presents an example of an ecological model for medication adherence (39). It classifies determinants of medication adherence into four categories (levels), namely: patient, micro, meso and macro. On the macro policy level, for example, access to healthcare (e.g. drug dispensing) with its dimensions of availability, affordability, accessibility, adequacy and appropriateness can play a significant role and has a direct effect on the patient's adherence to health behaviors (e.g. medication-taking). **Ecological models of health behaviors emphasize the environmental and policy contexts of behavior, while at the same time integrating social and psychological influences** (40). Remarkably, although these factors may be easily categorized and labelled, they must be regarded as dynamic and interacting, rather than as separate or layered. As such, ecological models have more utility than health behavior theories as a functional starting point for understanding the

behavior and developing multicomponent interventions that target several of its determinants. In its conceptualization, the BRIGHT study used an ecological model of medication adherence into which the IMBP was embedded.



*Figure 1.2: An ecological model for medication adherence;
Berben et al. 2012*

1.4 Pharmacologic treatment adherence

1.4.1 Medication adherence: definition and taxonomy

Medication (pharmacologic treatment) adherence is defined (41) as “the process by which patients take their medications as prescribed”. **A taxonomy that describes adherence to medication (29) conceptualizes it as a process with three major components (phases), namely initiation, implementation and persistence.** After being prescribed a medication, this process starts with treatment initiation, when the patient administers the first dose of the prescribed drug. Problems related to initiation of medication typically occur in the form of late or non-initiation, and they are collectively called primary or initial medication non-adherence (42). Implementation is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken (29). Suboptimal implementation of the dosing regimen can happen in the form of deviations from the prescribed dose or dose timing. Persistence refers to the length of time between initiation and the last dose (29). Persistence problems take the form of early discontinuation of the treatment without a physician's order.

1.4.2 Medication adherence research and its current state

While the first recorded observation of treatment non-adherence dates back to 350 BC (43), records of peer-reviewed publications in the late modern era show that it has been a topic of research for over five decades since the early 1960s. It has been investigated in many disease

areas and its scope has encompassed many focus points including, for example, conceptualizing and defining the construct (29), developing appropriate measurement methods and measures (44), describing the prevalence of MNA (9, 45), determining its correlates (46, 47) and consequences (15, 48) and developing interventions to circumvent the MNA problem (49). MNA as a health behavior, however, is a latent construct that represents a challenge to research precisely.

A major obstacle to progress in medication adherence and adherence-enhancing intervention research is, indeed, the inconsistency (50-52) in conceptualizing, defining and measuring the behavior and, accordingly, in analyzing and reporting the measured behavior. As a starting point, inconsistency in conceptualizing medication adherence hinders an understanding of the actual behavior being investigated. This is often the result of the common fallacy that medication adherence is a single and static construct (53). Logically, however, medication-taking is a set of several phases (as explained earlier in the taxonomy) with correspondingly numerous measurement methods and instruments to measure the behavior. Many researchers fail to separate these three phases when conducting research on adherence to medication. Consequently, defining, measuring, analyzing and reporting the behavior all suffer from inconsistencies. As a result, progress in medication adherence and adherence-enhancing intervention research has been impeded. Many intervention studies fail to raise the level of medication adherence (50) and many of those that do succeed fail to show corresponding improvement in outcomes (54).

Pooling medication non-adherence rates in a meta-analysis such as the one mentioned above (4) is an example of the problem, as it combines different measures and operational definitions of MNA in pooled estimates that oversimplify the reality. As a matter of fact, in the same meta-analysis, investigating 513 studies revealed the use of 6 categories of measurement methods. Indeed, medication adherence measurement methods are broadly classified as direct or indirect, each class has various categories, and, respectively, each category has various measurement instruments (measures) (16, 55, 56). **MNA rates that are based on different measurement methods and operational definitions are not directly comparable** (57). As indicated by Gellad et al. (57), comparing studies reporting prevalence of non-adherence to medications necessitates a clear definition and consistent measurement of the behavior. This will lead to appropriate analysis and clear reporting of the results of the analysis. Thus, proper inferences can be made based on clearly reported results.

1.4.2.1 Medication adherence research reporting & reporting guidelines

As explained above, inconsistency in conceptualizing, defining, measuring and analyzing medication adherence data leads to suboptimal reporting of the behavior. Indeed, several peer-reviewed publications have highlighted the need for more consistent and

transparent reporting of medication adherence research results (50, 51, 58-60). Although not specifically examined in this field, other health research reporting guidelines were shown to improve the quality of research reporting (61-63). Special guidelines for reporting medication adherence research have been developed before (42, 50, 64-66). Nevertheless, the quality of medication adherence research reporting is still unsatisfactory. This might be the result of a failure to adhere to the existing guidelines. In fact, a general theme was observed in a review of systematic reviews on adherence to reporting guidelines, in that 86% of the studies reported suboptimal levels of adherence to reporting guidelines (67).

However, the current guidelines for medication adherence research have shortcomings that might also contribute to the present suboptimal reporting of this research. First, they do not build on a clear conceptualization of medication adherence that helps researchers to report their target medication-taking behavior transparently (50, 64-66). In addition, they show some overlap with the guidelines developed for general health research and thus do not have medication adherence research as their exclusive focus (64, 65). Moreover, they sometimes focus on the conducting of a study rather than on reporting its results (42, 50, 66). As a result, there is a need to develop a guideline specific to reporting medication adherence research that builds on a taxonomy such as the aforementioned as a starting point for consistent and transparent reporting (68). **Based on this identified knowledge gap, this dissertation will propose a new guideline that remedies the shortcomings of the existing ones. Transparent reporting of medication adherence research will hopefully lead to the generation of more informative results that can be used to improve patient outcomes.**

1.4.3 Medication adherence after heart transplantation

Beyond reporting medication adherence research, HTx recipients represent a particularly susceptible patient population that has to follow a complex lifelong medication regimen. One study showed that, on discharge from hospital post-HTx, the mean total number of medications HTx recipients were taking was 14.3 (69), and at five years' post-HTx, about 32% of the recipients took 16 medications or more (69), many of which are administered more than once daily. Most importantly, many of these medications are long-term and are crucial for their transplanted heart (immunosuppressants) and their other chronic conditions/comorbidities. As far as immunosuppressants are concerned, research on the HTx-recipient population has shown that minor deviations from the immunosuppression schedule represent a risk factor for late acute rejections (28). In a five-year follow-up of 101 patients, HTx recipients who did not adhere to their immunosuppressants had significantly higher rates of cardiac graft coronary artery disease (53.3% vs. 40.9% for adherent HTx recipients) and higher, yet non-significant, rates of late acute rejection (11.8% vs. 2.4%), re-transplantation

(13.3% vs. 2.5%) and mortality (11.8% vs. 10.7%) (11). With regard to other post-HTx long-term medications, non-adherence to antidiabetics and antineoplastics, medications for two of the most common post-HTx complications, was found to be associated with higher morbidity, mortality and resource use (70-72). **Nevertheless, medication non-adherence in HTx is prevalent and has been observed since the early days of HTx development (73) and continues today (74).**

1.4.3.1 Post-HTx adherence to immunosuppressants and co-medications

Despite the recognized relationship between all post-HTx medication (immunosuppressants and co-medications) and HTx recipients' outcomes (11, 28, 41), research investigating adherence to all post-HTx medication is limited. Four studies (75-78) investigated MNA prevalence to co-medications separately yet without clarifying the actual phase of medication adherence investigated, a factor that impeded the identification of a target behavior for further research. One study (79) investigated self-reported implementation non-adherence to all medication in HTx recipients and found an overall implementation non-adherence prevalence of 36.7% and 39.2% to immunosuppressants and co-medications respectively. However, this study investigated medication non-adherence in HTx recipients at a single center. This limits the generalizability of the results to the global HTx-recipient population. **A study comparing non-adherence rates to immunosuppressants and co-medications in a diverse international sample of HTx recipients, while specifying the phase of adherence studied, could provide a detailed adherence profile of the post-HTx pharmacologic treatment. This would support decision-makers in their choice of adherence-enhancing interventions. This dissertation aims to cover this knowledge gap.**

1.4.3.2 Pre- and post-HTx adherence management practice patterns

As discussed above, ecological models of health behaviors provide a wide-ranging view of factors affecting the behavior. On the level of the healthcare organization providing post-HTx follow-up care (meso-level), structural attributes of the setting and its care processes contribute, directly and indirectly, to the outcomes of HTx recipients (80). With regard to MNA, the healthcare organization can affect the behavior through its contribution to the process of “management of adherence” (29). Illustrated in **figure 1.3**, management of adherence is defined as “the process of monitoring and supporting patients' adherence to medications by health care systems, providers, patients and their social networks” (29). As shown in the figure, this process spans the continuum of medication-taking from the first to the last prescription and its correspondingly necessary medication adherence.

This process is particularly important for HTx recipients in light of their complex medication regimen and of previous research showing that MNA to immunosuppressants post-HTx increases over time (28). As yet, it is not known how professional care for management of adherence is delivered along the HTx continuum internationally. **This dissertation will cover this knowledge gap by describing the international practice patterns of HTx centers with regard to management of adherence along the HTx continuum. Results from this study should provide further insights into opportunities for optimizing post-HTx healthcare delivery on the meso-level.**

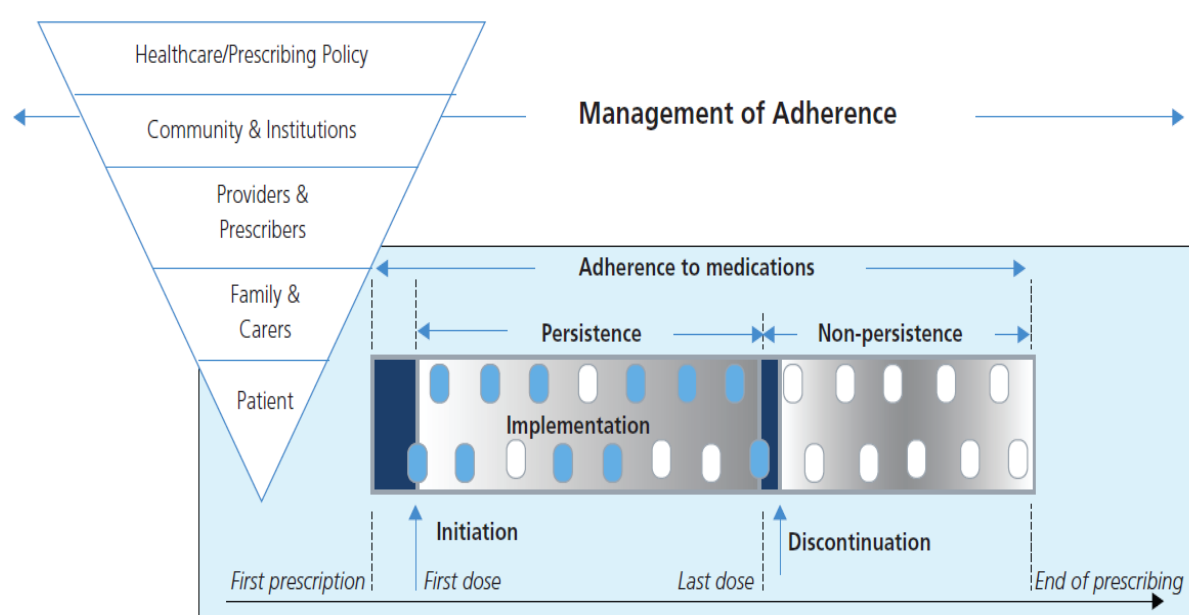


Figure 1.3: The process of adherence to medication and the process of management of adherence; Vrijens et al. 2012

1.5 Non-pharmacologic treatment adherence in heart transplantation

In order to prevent or delay the incidence of immunosuppressant-related side effects and other chronic conditions, lifelong follow-up and lifestyle modifications including weight control, physical activity, diet (e.g. low fat and low salt intake), abstinence from smoking or heavy alcohol intake and the use of sun protection are recommended for HTx recipients (24). In contrast to medication adherence, the evidence on non-pharmacologic treatment adherence in HTx is limited. Gaps in this topic include a lack of evidence-based guidelines for appropriate treatment doses (most of the existing guidelines are based on expert opinion) and a lack of appropriate and sensitive measures of adherence. This reflects on non-pharmacologic treatment non-adherence being far less studied in the population of HTx recipients.

Robust evidence of the prevalence of non-adherence to the post-HTx non-pharmacologic therapeutic regimen is scarce. A meta-analysis performed in 2007 (81) showed non-adherence rates of 33.7 cases per 100 patient-years for physical activity, 28.1 cases for following a diet, 8.5 cases for attending clinic appointments, 4.9 cases for alcohol use and 3.2 cases for tobacco use in HTx recipients. However, these estimates were based on a small number of available studies. Moreover, as clarified above in the case of medication adherence, pooling non-adherence estimates together raises a methodological issue because of the various operational definitions, measurement methods and sampling strategies used in the studies included in the meta-analysis.

Beyond this 2007 meta-analysis, other more recent studies have used small samples or samples from single centers (82), or have focused on a single behavior, providing no evidence of variations in HTx recipients' health behaviors between countries. **This dissertation will cover this knowledge gap by describing the international prevalence and variability of non-adherence to the post-HTx non-pharmacologic treatment regimen, using consistent methodology. Describing non-adherence prevalence in a diverse multinational sample of HTx recipients allows a better understanding of target behaviors for adherence-enhancing interventions and complements the post-HTx medication adherence profile.**

1.6 Summary and synthesis of the knowledge gaps

In summary, patients with chronic conditions usually follow a complex treatment regimen. HTx recipients represent an interesting subpopulation of chronically ill patients as their treatment encompasses a wide range of components including the following: administering many medications (polypharmacy), adopting certain lifestyles, following up with a professional healthcare giver, self-monitoring and self-management. Given the complexity and longevity of the treatment regimen, the problem of treatment (pharmacologic and non-pharmacologic) non-adherence arises. Certain knowledge gaps in the literature have been identified above and are used as the basis for this dissertation. Below, these knowledge gaps are summarized and the rationales for filling them are presented.

First, numerous studies have been conducted in attempts to describe MNA, determine its predictors (modifiable and non-modifiable) and outcomes, and design interventions to solve the problem by targeting its modifiable risk factors. Nonetheless, **many studies in medication adherence research lack a rigorous conceptualization of the construct (MNA), leading to suboptimal reporting of research results and a severe limitation of the usefulness of the results.** The lack of medication adherence

research reporting guidelines that are built on a clear conceptualization contributes to this problem, and developing such a guideline is envisioned as an essential step in enhancing the transparency of reporting medication adherence research and, consequently, its utility.

Second, HTx recipients' pharmacologic treatment regimen consists of immunosuppressants and other long-term medication. After HTx, immunosuppressants usually become the focus of professional and non-professional healthcare as the key to preserving the cardiac graft and hence, patients' lives. Nevertheless, death with a functioning graft is not uncommon among HTx recipients as a result of other comorbidities that develop before or after HTx. Based on the established relationship between medication adherence and clinical outcomes, ensuring adequate adherence to all post-HTx medication is essential. To date, **no study has described MNA to immunosuppressants and co-medication in a representative sample of the international HTx-recipient population while defining the actual phases and dimensions of MNA that are being studied.** Filling this gap would allow us to form a better understanding of the post-HTx medication adherence profile that could work as a starting point for developing adherence-enhancing interventions specific to the phases and dimensions in which MNA occurs.

Third, other factors beyond patients' control can affect their medication adherence behavior, according to the ecological model of medication adherence. Factors related to the healthcare organization providing post-HTx follow-up care include the organization's care processes. Previous research has shown that MNA to immunosuppressants post-HTx increases over time, **yet it is not known how the process of management of adherence by HTx follow-up clinicians is carried out internationally along the HTx continuum.** Describing international practice patterns among HTx centers concerning management of adherence along the HTx continuum would provide further insights into opportunities for improvement in post-HTx healthcare delivery, with the aim of enhancing medication adherence and, ultimately, HTx-recipients' outcomes.

Finally, HTx recipients' medication regimen is complemented by professional follow-up and a range of lifestyle modifications (non-pharmacologic treatment regimen). As there is an established relationship between non-adherence to this treatment regimen and poorer HTx-recipients' outcomes, it is envisioned that supporting HTx recipients with their non-pharmacologic treatment regimen could contribute to better HTx-recipients' outcomes. To date, **no study has provided a broad view of non-adherence to the post-HTx non-pharmacologic treatment regimen in an international sample, using uniform methodologies.** Describing non-pharmacologic treatment non-adherence in an international sample could help decision-makers to prioritize their target behaviors for adherence-enhancing interventions.

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Chapter

2

Research aims

Research aims

Given the highlighted knowledge gaps, the aims of this dissertation are:

1. To develop guidelines for reporting medication adherence research (Chapters 3 & 4)
2. To assess and compare the prevalence of medication non-adherence (MNA) (implementation and persistence phases) to immunosuppressants and co-medications in heart transplant (HTx) recipients (Chapter 5)
3. To describe the international practice patterns with regard to medication adherence assessment methods and intervention strategies across the transplantation continuum at HTx centers (Chapter 6)
4. To assess the international prevalence and variability in non-adherence to six components of the post-HTx non-pharmacologic treatment (physical activity, sun protection, diet, alcohol use, non-smoking, and outpatient follow-up visits) (Chapter 7)

Chapter

3

ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): A reactive-Delphi study protocol

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ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): A reactive-Delphi study protocol

Abstract

Introduction: Medication adherence is fundamental to achieving optimal patient outcomes. Reporting research on medication adherence suffers from some issues—including conceptualisation, measurement and data analysis—that thwart its advancement. Using the ABC taxonomy for medication adherence as the conceptual basis, a steering committee of members of the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP) launched an initiative to develop ESPACOMP Medication Adherence Reporting Guidelines (EMERGE). This paper is a protocol for a Delphi study that aims to build consensus among a group of topic experts regarding an item list that will support developing EMERGE.

Methods and analysis: This study uses a reactive-Delphi design where a group of topic experts will be asked to rate the relevance and clarity of an initial list of items, in addition to suggesting further items and/or modifications of the initial items. The initial item list, generated by the EMERGE steering committee through a structured process, consists of 26 items distributed in 2 sections: 4 items representing the taxonomy-based minimum reporting criteria, and 22 items organised according to the common reporting sections. A purposive sample of experts will be selected from relevant disciplines and diverse geographical locations. Consensus will be achieved through predefined decision rules to keep, delete or modify the items. An iterative process of online survey rounds will be carried out until consensus is reached.

Ethics and dissemination: An ethics approval was not required for the study according to the Swiss federal act on research involving human beings. The participating experts will be asked to give an informed consent. The results of this Delphi study will feed into EMERGE, which will be disseminated through peer-reviewed publications and presentations at conferences. Additionally, the steering committee will encourage their endorsement by registering the guidelines at the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network and other relevant organizations.

Strengths and limitations of the study

- Incorporates the input of many topic experts across various disciplines and geographical areas.
- Preserves subject anonymity and reduces the effect of dominant individuals.
- Uses statistical analysis techniques to reduce the potential of group pressure for conformity.
- Requires large blocks of time to administer several survey rounds and consolidate their output.
- Has potential to mould opinions based on the received aggregate feedback.

Introduction

Reporting research on medication adherence is suboptimal. Confusion prevails regarding the conceptual underpinning, adequate measurement, and analysis of medication adherence data, hindering scientific progress in this field [1, 2, 3]. Guidelines on the reporting of health research aim at enhancing publication quality and may focus on specific study designs, research areas, or sections of a report. Examples of such guidelines can be found on the website of the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network (www.equator-network.org), and include STROBE [4] (for observational studies in epidemiology), CONSORT [5] (for trials), and TIDieR [6] (for description and replication of interventions) guidelines. The introduction of such guidelines and their endorsement by professional societies and journals have proven to be helpful in enhancing the transparency and accuracy of health research reporting [7, 8].

There are existing published guidelines and recommendations focusing on medication adherence research [1, 9-12]. However, these guidelines overlap considerably with those developed for general clinical research and are, thus, not particularly specific for medication adherence research [9, 10]. Additionally, they do not build on a clear conceptualization of medication adherence [1, 9, 10, 12], and focus on study design rather than reporting [1, 11, 12]. Considering the shortcomings of the existing guidelines and the aforementioned deficits in the quality of medication adherence research, this field would benefit from specific reporting guidelines to boost the quality of reporting medication adherence research.

A steering committee of members of the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP, www.espacomp.eu) launched an initiative to develop ESPACOMP medication adherence reporting guidelines (EMERGE) that will tackle the abovementioned shortcomings in the following manner. Considering the conceptualization of medication adherence, the anticipated guidelines will build on the *ABC taxonomy for medication adherence* [13]. This taxonomy defines medication adherence as ‘*the process by which patients take their medications as prescribed*’. It divides this process into three interrelated phases: (1) initiation; (2) implementation; and (3) persistence, each demanding a clear operational definition and appropriate measurement and data analysis. Hence, setting this conceptualization as a standard for reporting medication adherence research is anticipated to remove the ambiguity surrounding medication adherence as a concept. Additionally, designing the guidelines attentively to avoid overlapping with the existing guidelines for general clinical research has a twofold benefit. First, it will steer clear of redundancy and, thus, any confusion that might arise accordingly. Second, it will allow the new guidelines to be applied to the different study designs and used in parallel with the general guidelines available for the corresponding study design. Finally, developing the guidelines as reporting guidelines

will help both the authors in figuring out the important elements to be reported about their research and the reviewers in critically appraising the quality of the studies.

Developing reporting guidelines, however, requires input by experts from various scientific backgrounds and needs to be relevant across geographical regions. This is particularly applicable in the context of medication adherence, which is a multidisciplinary science ranging from behavioral sciences through statistics and clinical medicine to economics. Delphi methodology, as a means for consensus building [14], enables integration of input from a wide variety of experts. It achieves consensus through an iterative process of survey rounds, providing the opportunity for participants to revise their input in subsequent rounds based on collective group feedback from previous rounds. This method enables the neutral and efficient integration of feedback from different experts, is suggested as one of the 18 steps put forward by the EQUATOR network in their guidance on developing health research reporting guidelines [15] and has been used in developing many similar guidelines [16, 17].

This approach has many benefits [18, 19, 20]. First, the iterative nature of the study and the feedback process allows participants to reassess their initial judgments. Thus, consensus is reached through a gradual stepwise process based on rational thinking and input. Second, participants do not interact directly and remain anonymous to each other until the survey rounds end. Hence, group domination by the views of certain individuals is avoided. Third, when participants consider changing or sticking to their original opinion after checking group response, this decision is not affected by the desire to be seen concordant with senior or dominant individuals. Fourth, experts can participate asynchronously and do not need to be present together while answering surveys as they receive collective feedback along with new surveys, which can be conducted through a web-based platform. Accordingly, it is feasible to use this approach to involve geographically distant participants. Moreover, the controlled feedback minimizes the effect of noise, which can happen in face-to-face group discussions. Finally, the ability to use statistical analysis facilitates reaching a more objective consensus than that usually reached through face-to-face conversations. Consequently, the Delphi method is an appropriate method to include the knowledge of many experts to cover the numerous aspects of the medication adherence subject.

Aim

The aim of this Delphi study is to build consensus among a group of topic experts regarding an item list that will support developing guidelines for medication adherence research reporting.

Methods and analysis

Overview of the study design

The study implements a reactive-Delphi design [21] where a group of medication adherence experts will be provided, in the first survey round, with an initial list of 26 items that are specific to medication adherence research. They will be asked to rate the relevance and clarity of the items (on a scale from 1 to 4; 1 is the lowest relevance/clarity, 4 is the highest relevance/clarity), with a possibility of providing suggestions of modifications of the initial items, or new items to be added. After each round of survey, pre-defined decision rules will be applied to keep, delete, or modify the items. This reactive-Delphi design allows for reduction of effort needed from the experts and faster arrival at consensus compared to the traditional Delphi design where experts are asked to come up with all items themselves.

The steering committee

The committee driving this initiative to develop guidelines for reporting research on medication adherence (also the authors of this study protocol) are members and founding members of ESPACOMP. One of their major research interests is medication adherence. They represent a diversity of disciplines including biostatistics, health economics, health policy and management, health services research, medicine, nursing, pharmacy, pharmacology, and psychology. Some members of the committee were involved in development of the *ABC taxonomy for medication adherence* (BV, DH, and SDG).

Role of the steering committee

The steering committee developed the initial items and will select the sample of experts for this study. Based on the decision rules, the steering committee will also apply the corresponding actions after each survey round: (i) keeping or deleting an item based on relevance scores, and (ii) modifying the wording of items based on clarity scores and the suggestions provided by the experts. For items that will not have achieved consensus on relevance after the survey rounds will be stopped, the steering committee will decide on each item individually based on internal consensus among its members, taking into consideration the aggregate input provided by the expert panel. All of the abovementioned tasks of the steering committee are further detailed later in this protocol.

Sample and sampling procedures

A purposive sample of medication adherence experts will be included in the study. The size of the group of experts needed for participation in any Delphi study does not depend on statistical power as representativeness in such studies is assessed based on the quality of the

sample rather than its size [20]. Accordingly, the steering committee identified medication adherence experts based on the representation of disciplines and geographical locations. In concordance with other similar projects aiming at developing guidelines for reporting of health research [16, 17], the goal is to include a minimum of 20 experts in the final survey round. To compensate for possible initial refusal or attrition over rounds, oversampling was considered with a rate of 25% per round. With a literature-based average [22] of three rounds until consensus is achieved, the starting sample will be a minimum of 40 experts.

More specifically, the Delphi participants need to be established experts in the field of medication adherence and satisfy all the following main selection criteria:

- 1)** having a minimum experience of five years in the field of medication adherence;
- 2)** having an established international profile in this field, recognized by scientific publications, policy reports and/or extensive participation in specialized topic conferences, meetings, or interest groups; and
- 3)** having good English proficiency to complete the surveys

To ensure representativeness of all relevant disciplines and geographical locations, the following variability selection criteria will be applied:

- 1.** The starting sample will include participants from each of the following disciplines:
 - a. Health services research
 - b. Clinical research
 - c. Statistics
 - d. Medicine
 - e. Nursing
 - f. Pharmacy/pharmaceutical sciences
 - g. Pharmaceutical industry
 - h. Clinical pharmacology
 - i. Pharmacoepidemiology
 - j. Behavioural medicine/health psychology
 - k. Journal editing
 - l. Public health
 - m. Health policy

- 2.** Geographical representation will be ensured by selecting experts from all continents.

Each of the steering committee members will provide suggestions for experts to be included on the expert panel for the Delphi study based on the aforementioned criteria. Feedback and agreement on the proposed list by the whole steering committee will be sought before experts are invited to participate. The final choice of the experts to be included will be based on an optimal distribution and representation of experts in view of the sample selection

criteria (main & variability criteria) and will be moderated by two members of the steering committee (SDG, RH). Delphi participants who will complete all rounds of the study will be listed in the final publication of the reporting guidelines in an acknowledgment section. However, the study will be fully anonymized and participants will not be known to each other during the survey rounds.

Generation of the initial item list

The initial item list was developed and fine-tuned by the steering committee. First, a literature review was performed to identify existing medication adherence research guidelines [9-11] and recommendations [1, 12] by two members of the steering committee (RH, SDG). This information was summarized and discussed in an in-person meeting in Prague in November 2015 among all of the steering committee members. This discussion, guided by the *ABC taxonomy for medication adherence* as well as by a review of common sections of the existing reporting guidelines for health research reporting (e.g. STROBE, CONSORT), led to generating a pool of items.

Using a stepwise review process, the steering committee reviewed and further fine-tuned the items in view of relevance and clarity over four feedback rounds via e-mail and conference calls. Items were gradually enhanced and revised to focus exclusively on aspects relevant to medication adherence. Redundancy between items of the existing reporting guidelines for health research (e.g. STROBE, CONSORT) and items for reporting research on medication adherence was scrutinized and eliminated where needed.

The resulting initial item list consists of 26 items distributed in two sections. The first section includes 4 items that reflect the conceptualization of medication adherence as put forward by the *ABC taxonomy for medication adherence* and represent the taxonomy-based minimum reporting criteria. The second section includes 22 items specific to medication adherence research reporting and organized in a way congruent with common sections of reporting guidelines for major study types (e.g. STROBE, CONSORT).

Decision rules and definition of consensus on relevance and clarity of items

Since the definition of consensus varies among Delphi studies according to the aims of each study, rating scales along with consensus rules for this study were inspired by the content validity index [23] as it simplifies the decision-making process as explained below. **Square (A)** in **figure 3.1** shows how the below decision rules will work together and their possible outcomes.

Item-level decision-making rules

Scores for *relevance* will be used to decide on keeping or deleting an item. Consensus on relevance of an item is defined as 70% of the experts in the sample giving this item a score of three or more on a scale from one to four (1: not relevant; 2: somewhat relevant; 3: quite relevant; 4: highly relevant) during any survey round. Hence, this item will be kept on the final item list. Consensus on irrelevance of an item is defined as 70% of the respondents giving this item a score of two or less during any survey round. Consequently, this item will be deleted from the item list.

Scores for *clarity* of wording will subsequently guide fine-tuning of the wording of the respective items to be included on the list. For simplifying the procedures, only one rule will be used for consensus on lack of clarity, defined as 70% of the respondents giving this item a score of two or less on a scale from one to four (1: not clear; 2: somewhat clear; 3: quite clear; 4: highly clear) during any survey round. Consensus on lack of clarity for any item will further lead to using comments provided by the experts to modify the wording of each corresponding item. This will be done by the steering committee after the rounds end.

List-level decision-making rule

One of the key methodologic criteria of Delphi studies is having a stoppage rule on when the survey rounds will stop [22]. For this purpose, a stoppage rule of having a consensus on relevance for 80% of all items on the list will be used. In other words, the Delphi rounds will be stopped once 80% of the items on the list at that point of time receive consensus on relevance (i.e. 80% of the items received a score ≥ 3 by 70% of the experts). This rule will be applied from the first round if no new items will be suggested or from the second round after the experts will have provided scores for any suggested new items.

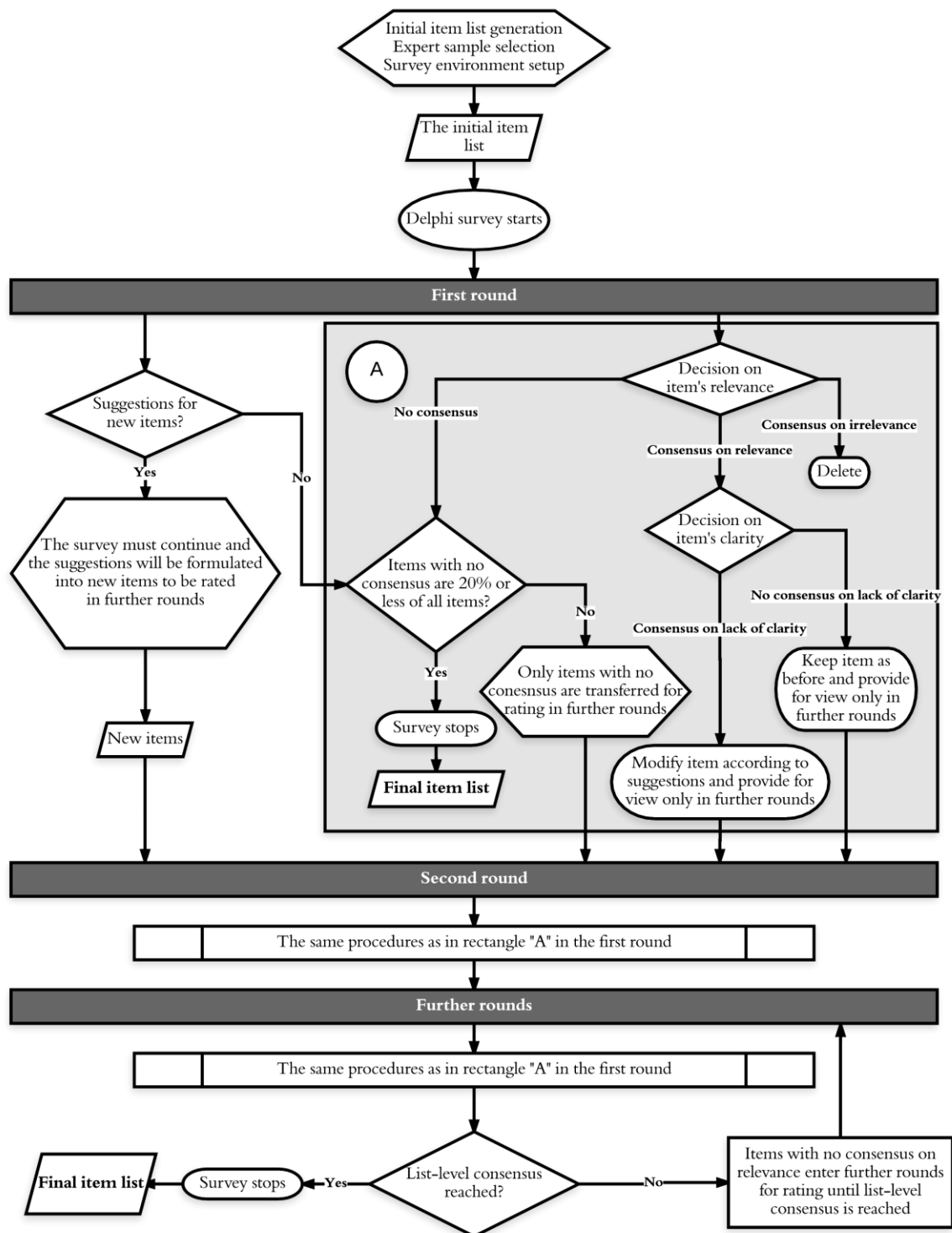


Figure 3.1: An overview of the Delphi process

Study procedures

Once the initial item list and the participants sample are ready, the study will start with a preparatory period of two weeks to set up the online environment of the survey and test its functionality. Afterwards, survey rounds will start and continue until the stoppage rule is fulfilled. An invitation for a feedback round will be sent to the expert group with a response deadline of two weeks after the invitation day. Reminders will be sent to those who won't respond, or will respond partially. Each round will be followed by an additional period for summarizing and analysing the responses and integrating the results into the following version of the survey. An invitation for a next feedback round will be sent out as described before to experts who will have completed all rounds from the beginning until then.

The surveys will be conducted and the responses will be collected online via a survey platform (SurveyMonkey®). Two member of the steering committee (SDG, RH) will be responsible for data collection and responding to possible inquiries from the experts. In case substantial issues are addressed by any member of the expert group, the other members of the committee will be consulted for advice and problem resolution.

A more detailed explanation of the process is provided below:

1. **First survey round** will consist of:

- a. providing a score for each of the items in view of *relevance* to the topic and *clarity* of wording
- b. justifying the scores chosen and/or suggesting modifications for each item – (*optional* – free-form text)
- c. suggesting additional new items – (*optional* – free-form text)

Additionally, experts will provide information on their demographics, professional background, and specific areas of expertise in adherence research for descriptive purposes as well as confirming their eligibility in the first survey round.

Scores provided for the items will be summarized by their percentages and frequency distribution and inclusion or deletion of items in the following version of the survey will be guided by the aforementioned decision rules. Comments on potential adaptations of item wording will be summarized and integrated by the steering committee where deemed relevant.

If no new items are suggested and consensus on relevance is reached for 80% of the items on the initial item list, the survey rounds will be stopped. Otherwise, the scores and comments of items that will not have reached consensus on relevance will be presented in the following round and/or suggestions of new items will be summarized

and integrated into the following version of the survey. Further evaluation and decision making will follow the methodology described before.

- 2. Second round:** An adapted item list including the scores and comments of the initial items as well as any new items from the 1st round will be sent to the experts. They will be invited to:
 - a. revise their opinion with new *relevance* and *clarity* scores, on the same scale as mentioned before, and comments for items that did not achieve consensus on relevance in the 1st round
 - b. score each of the new items in view of *relevance* to the topic and *clarity* of wording, on the same scale as mentioned before
 - c. justify the scores chosen and/or suggest modifications for each item – (optional – free-form text)

If list-level consensus is not reached by the 2nd round, scores and comments will be summarized as described in the 1st round and integrated into the item list to be presented in further rounds until consensus is reached.

- 3. Further rounds** will consist of presenting consolidated feedback for all items that will not have achieved consensus on relevance in previous rounds with a chance for experts to revise their opinion accordingly with:
 - a. new *relevance* and *clarity* scores for the remaining items
 - b. justification for the scores chosen and/or modifications for each item – (optional – free-form text)

Finally, results of the final round will be consolidated and presented to the steering committee for proceeding with further steps. The flowchart in **figure 3.1** delineates the survey rounds based on the input and output of each round.

Ethical and legal considerations

Since this study does not use health data of individuals, an ethics approval is not required according to the Swiss federal act on research involving human beings. Participants in the Delphi study will be asked to provide informed consent to have their responses included in further analysis and dissemination of the results. Furthermore, they will be informed about confidentiality of the data and the corresponding legal obligations of not exposing such data to third parties. Additionally, they will be asked whether they would like to be acknowledged in the corresponding publications and dissemination of the guidelines. All data relevant to the study will be kept on password-encrypted computers which can be accessed by the steering committee only.

Further planning of guidelines development

The list of items reached through this study will be integrated by the steering committee into the planned ESPACOMP medication adherence reporting guidelines (EMERGE). The guidelines will be disseminated through peer-reviewed publications, presentations at conferences of ESPACOMP and other relevant organizations, and registration of the guidelines with the EQUATOR Network. Endorsement of the guidelines by journals and relevant professional organizations will be encouraged. Two members of the steering committee (SDG, RH) will remain available to receive feedback and criticism after publication. Accordingly, further updates and revisions of the guidelines will be considered on an annual basis during ESPACOMP annual meetings, based on the EQUATOR guidance for developers of health research reporting guidelines.

Outlook

Medication nonadherence is a public health threat that causes poor patient outcomes and increased economic burden[24, 25]. The quality of medication adherence research as well as the quality of its reporting will determine the development and testing of effective and innovative solutions to enhance patients' adherence to medications and is therefore of paramount importance to many stakeholders. EMERGE aim at guiding researchers to report relevant aspects of medication adherence research in a standard manner. The use of the guidelines, in combination with other existing guidelines like STROBE or CONSORT, is expected to facilitate this task and, subsequently, help research in medication adherence field advance towards achieving its ultimate goal of improved outcomes.

Delphi study status

The initial item list was developed and the online survey environment was set up and tested by the steering committee. The sample of experts was chosen and data collection (1st round) started in June 2016.

Contributors

All persons listed as authors contributed to preparing the manuscript and the International Committee of Medical Journal Editors (ICMJE) criteria for authorship were met. Specifically, the following contributions were made by the respective authors: RH contributed substantially to the conception and design of the study, and the acquisition, analysis, and interpretation of data for the work; drafted the work and revised it critically; approved the final version to be published; agrees to be accountable for all aspects of the work. JD-J, DAH, BV, IBW and LLZ contributed substantially to the acquisition, analysis and interpretation of data

for the work; revised the work critically; approved the final version to be published; agree to be accountable for all aspects of the work. SDG is the project's principal investigator who contributed substantially to the conception and design of the study, and the acquisition, analysis, and interpretation of data for the work; drafted the work and revised it critically; approved the final version to be published; agrees to be accountable for all aspects of the work.

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Competing interests

None declared.

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Chapter 4

ESPACOMP Medication Adherence Reporting Guideline (EMERGE)

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ESPACOMP Medication Adherence Reporting Guideline (EMERGE)

Abstract

Research on assessing or managing medication adherence applies approaches from observational, interventional, and implementation science that spans many disciplines and demands coherent conceptualization, valid methods, appropriate analyses, and complete and accurate reporting. To ensure such reporting, the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) recommends standard reporting approaches based on an accepted taxonomy.

This guideline is derived from a literature review, a reactive Delphi study with 26 medication adherence experts from many countries and disciplines, and feedback from ESPACOMP members. It is designed to supplement existing guidelines for health research reporting and is structured around 4 minimum reporting criteria and 17 items reflecting best reporting practice. By enhancing and harmonizing research reporting, EMERGE aims to advance research and, ultimately, patient outcomes.

Medication nonadherence is a major public health problem (1, 2), with significant health and economic consequences (1-4). For many conditions, taking medications as prescribed is crucial to achieve optimal outcomes (5-7). Despite more than 50 years of research, the evidence base for effective interventions that can be implemented in routine clinical care remains limited (8, 9).

Research related to medication adherence applies approaches from observational, interventional, and implementation science across disciplines, including but not limited to medicine, pharmacy, nursing, behavioral science, sociology, pharmacometrics, biostatistics, and health economics (10). Unfortunately, inadequate research reporting often hampers interpretation of findings, complicates data abstraction for meta-analyses, and prevents study replication. Common problems include unclear or inconsistent definitions (11-14), inadequate measurement of adherence outcomes (7, 14, 15), suboptimal analyses (11-14), insufficient description of intervention delivery settings (15), and scant theoretical underpinnings (16).

Previous efforts to improve reporting standards in adherence research (11, 17-20) have resulted in guidelines and recommendations that overlap with existing guidelines for health research reporting, such as CONSORT (Consolidated Standards of Reporting Trials) (21), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (22), and StaRI (Standards for Reporting Implementation Studies) (23). These recommendations deviate from an exclusive focus on medication adherence research (17, 19), include no clear conceptualization of medication adherence (11, 17, 19, 20), and are more concerned with conducting rather than reporting research (11, 19, 20).

Weighing these shortcomings against evidence that guidelines endorsed by professional societies and journals enhance overall health research reporting (24-28), the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP; www.espacomp.eu) developed the ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Grounded in the conceptualization of medication adherence provided by a previously reported taxonomy (10), EMERGE aims to complement existing guidelines for health research reporting. It aims to increase the transparency and consistency of reporting by guiding researchers through processes specifically relevant to medication adherence.

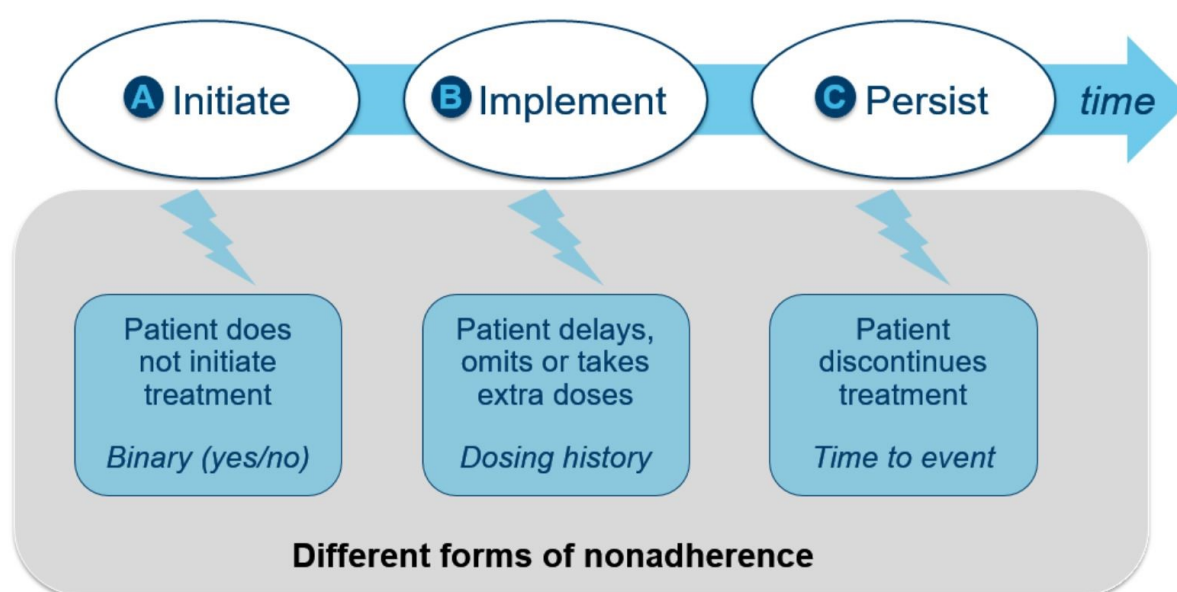
Taxonomy for Medication Adherence

EMERGE adopts the previously reported taxonomy (10), which defines medication adherence as “the process by which patients take their medications as prescribed” and divides it into 3 interrelated yet distinct phases: initiation, implementation, and persistence (**figure 4.1**). Medication nonadherence, such as late or incomplete initiation or non-initiation,

suboptimal implementation of the dosing regimen (for example, late, skipped, extra, or reduced doses or drug holidays), or early discontinuation (non-persistence), can occur in any of these phases. Each phase creates methodological challenges related to how medication use is operationally defined, measured, and analyzed.

ABC Taxonomy: Medication Adherence

The process by which patients take their medications as prescribed



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Vrijens et al., *Br J Clin Pharmacol* 2012;73:691-705.

Figure 4.1: Conceptualization of medication adherence

Development of EMERGE

EMERGE was developed in accordance with recommendations of the EQUATOR (Enhancing the QUALity and Transparency Of health Research) Network (www.equator-network.org) for developers of guidelines for health research reporting (29). The methods for developing EMERGE have been previously published (30). In brief, a steering committee comprising 7 members of ESPACOMP (S.D.G., L.L.Z., J.D.J., R.H., D.A.H., I.B.W., and B.V.) led the project. The committee first convened in Prague, Czech Republic, in 2015, followed by 4 rounds of feedback via e-mail and conference calls in 2016. It discussed a literature review of published adherence guidelines and a further review of existing reporting guidelines for health research (21-23, 31), yielding an initial pool of 26 items (that is, statements) organized per the sections of the reporting guidelines used most often (CONSORT and STROBE). To avoid redundancy and to facilitate EMERGE's applicability across study designs, the committee considered overlap with existing guidelines throughout the development process (30).

The initial 26-item pool was the basis of 2 rounds of reactive Delphi surveys (32, 33). The committee selected and invited a purposive sample of 45 international experts (from 15 countries and 6 continents) who represented diverse disciplines and fields engaged in medication adherence research (17 in clinical research, 14 in health services research, 13 in public health, 11 in medicine, 9 in behavioral medicine or health psychology, 6 in journal editing, 5 in health policy, 5 in pharmacoepidemiology, 5 in statistics, 4 in nursing, 4 in pharmacy or pharmaceutical sciences, 3 in clinical pharmacology, 2 in the pharmaceutical industry, and 6 in other fields; experts belonged to 1 or more disciplines). Of the 45 experts, 29 participated in the first round (response rate: 64%). They evaluated each item for relevance and clarity and could comment, suggest further items, or modify the initial items. Guided by predefined rules (30) and qualitative comments from the survey experts, the steering committee reviewed and discussed the first-round results during a meeting in Húsafell, Iceland, in July 2016.

Based on the agreed criteria, all 26 items evaluated in the first Delphi round were judged to be relevant (mean, 91% [SD, 5%] [range, 79% to 97%]) and clear (mean, 84% [SD, 10%] [range, 59% to 97%]). Nevertheless, the experts' qualitative comments and subsequent committee discussion presented opportunities to optimize the wording of several items. The committee excluded 5 items because of redundancy or inconsistency with other items from EMERGE or the main reporting guidelines.

The remaining 21 items entered the second Delphi round, during which 26 of the 29 experts (90%) who participated in the first round rerated the items for relevance and clarity. All items again cleared the threshold for relevance (mean, 93% [range, 85% to 100%]) and clarity (mean, 90% [range, 73% to 100%]). The qualitative comments allowed the committee to fine-tune the wording of several items, resulting in the 21-item list that was presented at the annual ESPACOMP conference in Lisbon, Portugal, in November 2016 and approved by a formal vote of all members.

The study was funded by ESPACOMP. The EMERGE steering committee is composed entirely of ESPACOMP members, who designed EMERGE, wrote this article, and submitted it for publication.

EMERGE

EMERGE comprises 21 items organized in 2 sections (**table 4.1**). The first section includes 4 items outlining the minimum reporting criteria for medication adherence research. The following criteria need to be specified clearly: each phase of medication adherence studied (that is, initiation, implementation, and persistence); a precise operational or working

definition of each examined phase; the methods of adherence measurement used for each phase, along with information on measure performance (that is, validity, reliability, and potential bias); and the results of the analysis relevant to each phase.

The second section of the guideline comprises 17 items that provide more detailed information on medication adherence reporting. These are organized according to the reporting guidelines for experimental and observational studies (that is, CONSORT and STROBE) (**table 4.1**). Building on the minimum reporting criteria, these items further highlight the importance of considering and distinguishing between the 3 phases of medication adherence (for example, items 3a-b [background or introduction], item 4a [study objectives or hypotheses], items 8a-b [statistical analysis], and items 10a-c [discussion]). Other items address areas that are often under- or unreported in adherence research. Item 3b, for instance, focuses on the need to clarify the rationale or framework guiding the study. Item 5a addresses information relevant to the setting where the study was done (such as characteristics of the health care system, health care organization, and health care team), and item 5c requests information on routine care related to the management of medication adherence. For intervention studies (items 7a-b), descriptions of both intervention and comparator groups are requested. Interventions should be described (if relevant) in the context of specified levels of the health care system (that is, patient or caregiver, health care provider, health care organization, and health care system). Further methodological details are requested pertaining to sampling (item 5b asks whether medication adherence is an eligibility criterion) and measurement (item 6a addresses the potential effect of the adherence measure on medication adherence). Information requested on statistical methods distinguishes between medication adherence as an outcome measure (item 8a) and its use as an explanatory variable (item 8b). Item 7b, which is relevant to implementation science, asks for information (when applicable) on any implementation strategy (34) that contributes to translation of a medication adherence intervention into clinical practice. EMERGE also reminds authors to include details in their results sections of how nonparticipation or dropout may relate to medication nonadherence (item 9a) or sample characteristics relevant to medication nonadherence (item 9b).

Table 4.1: ESPACOMP Medication Adherence Reporting Guideline

Item	Recommendation	Page/Line Number
Minimum reporting criteria		
1a	Phases of medication adherence: State the phase(s) of medication adherence studied (i.e., initiation, implementation, and persistence), and justify, where possible, focusing on this/these phase(s).	—
1b	Operational definition: Provide the precise operational/working definition for each phase of medication adherence studied (i.e., initiation, implementation, and persistence).	—
1c	Measurement: Specify the methods of measuring medication adherence (e.g., self-report, claims data, blood sampling, and electronic monitoring). Consider each phase studied (i.e., initiation, implementation, and persistence), with details on the performance of the measures, where applicable (e.g., validity, reliability, and potential bias).	—
1d	Results: Describe the results of the analysis appropriate to each phase of medication adherence studied (i.e., initiation, implementation, and persistence).	—
Additional EMERGE items		
Abstract		
2a	Present in the abstract, in as much detail as space permits, information on the 4 minimum reporting criteria (i.e., items 1a–1d).	—

Item	Recommendation	Page/Line Number
Background/introduction		
3a	Summarize what is known about the topic with appropriate reference to the phase(s) of medication adherence (i.e., initiation, implementation, and persistence).	—
3b	Describe the rationale and/or framework guiding the medication adherence study (e.g., theoretical framework and implementation science model).	—
Study objectives or hypotheses		
4a	State the study objectives or hypotheses with reference to the phase(s) of medication adherence studied and context (patient population and setting).	—
Methods		
Design and participants		
5a	Describe the setting in which the study was done. Refer to factors relevant to medication adherence, such as characteristics of the health care system, organization, and team.	—
5b	State whether medication adherence was an eligibility criterion (e.g., inclusion/exclusion). If so, define the measures and rules used.	—
5c	Describe routine care related to the management of medication adherence, if applicable (e.g., routine assessment of medication adherence, adherence support programs, and provider training).	—
Measurement*		
6a	Measurement methods can themselves affect medication adherence (e.g., questionnaires, blood sampling, and electronic monitoring). Address this problem as appropriate.	—

Item	Recommendation	Page/Line Number
Intervention (where applicable)		
7a	For intervention and comparator groups, describe each relevant level of the medication adherence intervention (e.g., health care system, organization, and provider and patient/caregiver).	—
7b	Describe any implementation strategy that contributes to the translation (e.g., uptake, delivery, and sustainability) of the medication adherence intervention in clinical practice, if applicable.	—
Statistical analysis		
8a	If medication adherence is an outcome variable, justify the statistical methods, given the characteristics of the variable (e.g., phases of medication adherence, data type, statistical distribution, data censoring, and longitudinal dependence).	—
8b	If medication adherence is an explanatory variable, describe how it is related to the outcomes (e.g., causal pathway and temporal sequence).	—
Results [†]		
9a	Determine whether nonparticipation and/or dropout are associated with nonadherence, and provide any relevant data.	—
9b	Present sample characteristics relevant to medication adherence (e.g., those related to sociodemographics and therapy, condition, patient, caregiver, and health care team/health care system).	—

Item	Recommendation	Page/Line Number
Discussion		
10a	Discuss study strengths and limitations with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, and persistence).	–
10b	Discuss the study findings in the context of existing evidence on medication adherence (e.g., theory, measurement, and intervention effects).	–
10c	Discuss the generalizability (external validity) of the study findings with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, and persistence).	–

ESPACOMP = European Society for Patient Adherence, COMpliance, and Persistence.

* See item 1c.

† See item 1d.

Discussion

EMERGE was developed to help researchers improve the often methodologically weak (8, 35, 36) and suboptimum reporting of medication adherence research (11-13). Although EMERGE has the advantage of being applicable to many study designs and methods focusing on medication adherence, authors will combine EMERGE items with other appropriate guidelines for health research reporting (such as STROBE, CONSORT, and StaRI).

EMERGE was developed through a consensus-based process involving a multidisciplinary group of international experts on medication adherence. Using the Delphi surveys, these experts provided 2 rounds of feedback on the relevance and clarity of each item. In addition to enhancing EMERGE's relevance across diverse settings, their cooperation will facilitate guideline implementation.

One of EMERGE's major strengths is its grounding in a medication adherence conceptualization provided by a robust taxonomy (10). Since its publication, this taxonomy has greatly benefited the field of medication adherence research (37, 38) and has been broadly adopted and widely cited (39). It distinguishes between 3 phases of adherence: initiation, implementation, and persistence. EMERGE highlights the need to acknowledge and specify each phase as a distinct part of the process by which patients manage their medication regimens; each requires specific considerations regarding conceptualization, definition, measurement, and analysis.

EMERGE items—with the 4 minimum reporting criteria at their core—reflect essential yet often poorly handled or omitted elements of medication adherence research reporting. These include omission or suboptimal definition of key terms (7, 11-13), use of suboptimal measures (15), and use of inappropriate analytic methods (11-13). EMERGE also highlights the need for other relevant and often neglected aspects of adherence research reporting, such as a clearly explained rationale or framework (16) and detailed information on the health care setting, including routine care (15).

EMERGE includes an item relevant to implementation science, which complements the StaRI reporting guideline (23), in recognition of the importance of this discipline in advancing the field of medication adherence. Although several promising interventions have been developed to improve adherence (8, 35, 40), none have been easy to implement in clinical practice. We do not suggest that every study can or should include an implementation component, but we encourage researchers to plan studies with an eye toward implementation and sustainability.

The main limitation affecting EMERGE's development is its primary focus on quantitative methods. However, the 4 minimum reporting criteria can also help those designing qualitative and mixed-methods research to align their focus and relevant methodological aspects with the adherence taxonomy (10). In addition, although user testing showed that EMERGE is easy to apply in combination with the main reporting guidelines, the advised combination might initially seem challenging. Following the 21 EMERGE items will yield thorough reporting of all matters common to medication adherence research, but journal word limits may sometimes restrict full reporting. Possible solutions include pre-publishing detailed methods and protocols and providing online-only supplements or appendixes. Finally, although we tried to guarantee representation of all continents, the international Delphi team included fewer experts from African and Asian countries.

In addition to this article, dissemination and use of EMERGE will be enhanced by information available on the EQUATOR and ESPACOMP Web sites (www.equator-network.org and www.espacomp.eu/emerge) and endorsed by a range of related journals and professional organizations. ESPACOMP will support regular updates of EMERGE to ensure timely propagation of lessons learned from its use, along with new developments in medication adherence science.

In conclusion, implementation of EMERGE is expected to enhance the reporting quality of medication adherence research by standardizing approaches, reducing research waste, accelerating progress in this and related fields, and ultimately improving patient outcomes.

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Chapter

5

Higher prevalence of medication non-adherence to co-medications than to immunosuppressants in heart transplant recipients: Findings from the international cross-sectional BRIGHT study

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**Higher prevalence of medication non-adherence to co-
medications than to immunosuppressants in heart transplant
recipients:
Findings from the international cross-sectional BRIGHT study**

Abstract

Purpose: To assess and compare the prevalence of medication non-adherence (MNA) (implementation and persistence) to immunosuppressants and co-medications in heart transplant (HTx) recipients.

Methods: MNA prevalence was assessed using BAASIS® (self-report) and compared using logistic regression in a 36-HTx-center 11-country 4-continent sample of 1397 HTx recipients.

Findings: MNA was significantly ($\alpha=0.05$) higher regarding co-medications than immunosuppressants (implementation: taking 23.9% vs. 17.3% (OR=1.5), drug holiday 5.7% vs. 1.9% (OR=3.17), dose alteration 3.8% vs 1.6% (OR=2.46) and discontinuation: 2.6% vs. 0.5% (OR=5.15)).

Implications: Given the prevalent MNA to all post-HTx medications, adherence-enhancing interventions need to focus on the entire medication regimen.

ClinicalTrials.gov identifier: NCT01608477

Background

Heart transplant (HTx) recipients depend on complex life-long medication regimens⁽¹⁾ of immunosuppressants to prevent graft rejection and co-medications (e.g., antihypertensives, lipid-lowering drugs) to help prevent or treat long-term co-morbidities. Previous research showed that HTx recipients' mean total number of medications at discharge post-HTx was 14.3⁽²⁾. Five years post-HTx, 32% of patients were taking 16 medications or more⁽²⁾, many administered more than once daily. Such a high treatment burden increases the risk of medication non-adherence (MNA)⁽³⁾. In solid organ transplantation⁽⁴⁾, MNA is defined as any "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" and is associated with suboptimal clinical and economic outcomes⁽⁴⁾.

As a process, medication adherence consists of three inter-related phases⁽⁵⁾: initiation, implementation, and persistence. For HTx recipients, initiation occurs during hospitalization for transplantation, making it irrelevant in the context of nonadherence. Implementation non-adherence involves multiple dimensions: taking (missing a dose or more); drug holiday (skipping ≥ 2 consecutive doses); timing (taking medication > 2 hours before or after the prescribed time); and dose alteration (taking more or fewer pills than prescribed or changing dosages without a physician's order).

While considerable transplantation research has been devoted to immunosuppressant non-adherence (NA), co-medication NA is less studied⁽¹⁾. Four HTx studies⁽⁶⁻⁹⁾ reported separate prevalence estimates of co-medication NA, but without distinguishing between the phases of adherence. This omission impedes identification of target behaviors for interventions. To the best of our knowledge, the only study⁽¹⁰⁾ to investigate the prevalence of implementation NA to both medication categories in HTx recipients reported overall implementation NA prevalence of 36.7% and 39.2% to immunosuppressants and co-medications respectively. However, that study's single-center design limited the generalizability of its results to the HTx population.

Accordingly, assessing MNA to immunosuppressant and co-medication implementation and persistence in a diverse sample of HTx recipients from various countries while distinguishing between the dimensions will clarify how HTx recipients manage their post-HTx medication regimens, while helping define target behaviors for adherence-enhancing interventions. Therefore, the central aim of this study is to describe and compare the prevalence of MNA (in the implementation and persistence phases) to immunosuppressants and co-medications in an international sample of HTx recipients.

Methods

This study is a secondary data analysis of the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study, a cross-sectional study in 36 HTx centers in 11 countries on 4 continents. Detailed information on the BRIGHT study's methodology is reported elsewhere(11).

Sampling and data collection

The data used for this analysis were collected via patient interviews during outpatient clinic visits. Using a stratified random sampling approach based on center size (number of annual HTx procedures), HTx recipients were eligible to participate if they were adults (≥ 18 years at enrolment), were transplanted and undergoing follow-up for routine care at a participating HTx center, received HTx as a single-organ transplant, were first-time HTx recipients (no re-transplantation), were 1–5 years post-HTx, were able to read and understand one of the languages in which the study was conducted, and were willing and able to provide written informed consent. HTx recipients were excluded if they had participated in adherence-intervention research or drug trials during the 6 months prior to inclusion or had received professional support for medication intake.

Variables and measurement

Implementation- and persistence-phase MNA were assessed during the patient interview (self-report) based on a recall period of four weeks for implementation and one year for persistence. The instrument used was the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS®)(12), which is built around the most recent taxonomy for medication adherence(5). Administered in a non-threatening, non-judgmental manner to encourage truthful answers, the BAASIS® starts by asking the patient's about their current immunosuppressant regimen, i.e., each medication's name, dose, dosing frequency, and intake schedule. The MNA assessment process is described below.

Assessment of MNA to immunosuppressants: Implementation is covered by 4 yes/no items: taking, drug holiday, timing, and dose alteration. Persistence is measured by asking patients if, during the recall period, they stopped taking their medication completely without physician's orders (yes/no).

Assessment of MNA to co-medications: The BAASIS® instrument was adapted for co-medications where taking, drug holiday and dose alteration are the only assessed implementation dimensions as timing is less critical for the majority of these medications. Persistence to co-medications was assessed as with immunosuppressants.

Scoring of the BAASIS®: Within each of the measured MNA dimensions, each positive answer indicated an instance of MNA. To indicate the prevalence of non-adherence within each dimension, we calculated the percentage of HTx recipients answering positively. Additionally, for immunosuppressants, a positive answer to any of the implementation dimensions indicated an instance of overall implementation NA (summarized similarly as a percentage).

Statistical analysis

Data were summarized descriptively based on levels of measurement and distribution (i.e., frequencies, proportions, means (SD)). To avoid over- or underrepresentation of each country's HTx recipient population, MNA prevalence was calculated as a weighted average. This was achieved by multiplying each national non-adherence prevalence by a weighting factor corresponding to the ratio of the HTx recipient population in the corresponding country to that of all included countries during the period of the study's data collection there (based on data from the Global Observatory on Donation and Transplantation, <http://www.transplant-observatory.org>).

To compare between immunosuppressant and co-medication NA prevalence (taking, drug holiday, dose alteration, and discontinuation), we used logistic regression analysis by generalized estimation equations, adjusting for data clustering on the HTx recipient and center levels. As fewer than 2% of data were missing, pairwise deletion was used. The significance level was set at 0.05. Stata® 13 (StataCorp LLC, Texas, USA) was used for descriptive statistics and SAS® 9.4 (SAS Institute Inc., North Carolina, USA) for regression analysis.

Results

From the 36 participating HTx centers, 2523 patients were eligible for inclusion. We randomly invited 1677 to participate, of whom 1397 (83.3%) responded. Their characteristics are shown in **table 5.1**. The observed and weighted prevalence of MNA for immunosuppressants and co-medications is reported in **table 5.2**.

Table 5.1: Sample characteristics

Characteristic	Value
Age (N)	1380
Years, mean (SD)	53.7 (13.2)
Gender (N)	1390
Male, n (%)	1011 (72.7%)

Characteristic	Value
Ethnicity (N)	1381
Caucasian, n (%)	1186 (85.9%)
Education (N)	1377
Primary school, n (%)	187 (13.6%)
Secondary school, n (%)	426 (30.9%)
Further education, n (%)	294 (21.4%)
University, n (%)	470 (34.1%)
Employment status (N)	1391
Employed, n (%)	413 (29.7%)
Marital status (N)	1387
Single, n (%)	242 (17.5%)
Married/cohabiting, n (%)	955 (68.9%)
Divorced/separated, n (%)	149 (10.7%)
Widowed, n (%)	41 (3%)
Time post-HTx (N)	1395
Years, mean (SD)	3.4 (1.4)
Immunosuppressants (N)	1389
<u>Calcineurin inhibitors</u>	1325 (95.4%)
Tacrolimus, n (%)	879 (63.3%)
Cyclosporine, n (%)	452 (32.5%)
<u>IMDH inhibitors</u>	1127 (81.2%)
Mycophenolate, n (%)	1066 (76.7%)
Azathioprine, n (%)	61 (4.4%)
<u>Corticosteroids</u>	710 (51.2%)
Prednisolone, n (%)	698 (50.3%)
Hydrocortisone, n (%)	13 (0.9%)
<u>mTOR inhibitors</u>	263 (19%)
Everolimus, n (%)	199 (14.3%)
Sirolimus, n (%)	64 (4.6%)
N: number of patients with observations for the corresponding variable	
SD: standard deviation	
IMDH: inosine monophosphate dehydrogenase	
mTOR: mechanistic target of rapamycin	

Table 5.2. Prevalence and comparison of medication non-adherence (MNA), implementation and persistence phases, to immunosuppressants and co-medications

Adherence dimension	Immunosuppressants				Co-medications				Logistic regression results		
	Prevalence of MNA (BAASIS®) ^a			95%CI ^b	Prevalence of MNA (BAASIS®) ^a			95%CI ^b	OR	95%CI	P value
	n / N	% (observed)	% (weighted)		n / N	% (observed)	% (weighted)				
Implementation^a											
<i>Taking dimension</i>	241/1392	17.3%	15.1%	13.2%-17.0%	333 / 1392	23.9%	21.2%	19.0%-23.3%	1.50	1.30-1.73	<0.0001
<i>Drug holiday dimension</i>	26/1392	1.9%	1.4%	0.8%-2.0%	79 / 1392	5.7%	5.1%	3.9%-6.2%	3.17	2.13-4.73	<0.0001
<i>Timing dimension</i>	395/1376	28.7%	26.2%	23.9%-28.5%							
<i>Dose alteration dimension</i>	22/1387	1.6%	1.5%	0.8%-2.1%	53 / 1390	3.8%	4.0%	3.0%-5.0%	2.46	1.49-4.06	0.0004
<i>Overall implementation</i>	520/1392	37.4%	34.5%	32.2%-37.2%							
Persistence^b											
<i>Discontinuation dimension</i>	7/1386	0.5%	0.6%	0.2%-1.0%	35 / 1390	2.6%	2.4%	1.6%-3.2%	5.15	2.36-11.20	<0.0001

^a 1. Taking dimension (omitting a single dose once or more during the prior 4 weeks)

2. Timing dimension (taking the medication >2 hours before or after the prescribed taking time once or more during the prior 4 weeks, only for immunosuppressants)

3. Dose alteration dimension (altering the prescribed amount of medication once or more during the prior 4 weeks without a physicians' order)

4. Drug holiday dimension (skipping at least two consecutive doses once or more during the prior 4 weeks)

^b Discontinuation of medication use completely within the prior year without a physicians' order

BAASIS: Basel assessment of adherence to immunosuppressive medication scale, **OR:** odds ratio, **CI:** confidence intervals of the weighted estimates

Medication non-adherence to immunosuppressants

Calcineurin inhibitors were used by 95.4%, IMDH (inosine monophosphate dehydrogenase) inhibitors by 81.2%, corticosteroids by 51.2%, and mTOR (mechanistic target of rapamycin) inhibitors by 19% of the sample. Immunosuppressant implementation NA was observed in 37.4% of participants. More specifically, the immunosuppressant NA prevalence was 17.3% for taking, 1.9% for drug holiday, 28.7% for timing, and 1.6% for dose alteration. For discontinuation, we found a prevalence of 0.5%.

Medication non-adherence to co-medications

The prevalence of NA to co-medications was 23.9% for taking, 5.7% for drug holiday, 3.8% for dose alteration, and 2.6% for discontinuation.

Comparison between immunosuppressant and co-medication non-adherence

Overall we found significantly higher levels of NA to co-medications compared to that regarding immunosuppressants: taking (OR=1.50; 95%CI=1.30-1.73, $p<0.0001$), drug holiday (OR=3.17; 95%CI=2.13-4.73, $p<0.0001$), dose alteration (OR=2.46; 95%CI=1.49-4.06, $p=0.0004$), and discontinuation (OR=5.15; 95%CI=2.36-11.20, $p<0.0001$). Similar higher prevalence of co-medication NA was also observed at the national level in all countries and dimensions except the taking dimension in Belgium and Switzerland.

Discussion

This study showed, in a large international sample of HTx recipients, that post-HTx MNA is prevalent for both immunosuppressants and co-medications. Given the risk accompanying immunosuppressant NA vis-à-vis HTx outcomes(1, 2), and the limited forgiveness of immunosuppressants(1), this magnitude of MNA is worrisome and calls for interventions. Moreover, confirming the evidence from prior studies in HTx(3) and other transplant populations(4), we found a significantly higher prevalence of MNA to co-medications than to immunosuppressants. A study in kidney transplant recipients(4) proposed the concept of self-regulation as an explanation, i.e., patients might classify their drugs according to their indication to two categories (strict vs. flexible) and adjust their medication intake accordingly based on the daily pill burden. This adjustment/regulation process is conceptualized(5) as a function of the representation of health threats, the targets set accordingly for ongoing coping, the procedures to regulate these targets, and the appraisal of coping outcomes. Whether this self-regulation model sufficiently explains the observed adherence differences remains to be confirmed.

This study has some limitations. First, given the main study's many variables and large sample, MNA was measured via self-report, which is susceptible(6) to social desirability and memory biases. Second, the main study's focus was on immunosuppressants. Accordingly, detailed data on individual co-medications (e.g., number and names of drugs, daily pill burden) were unavailable for this secondary analysis. For the same reason, investigating factors responsible for differences between immunosuppressant and co-medication NA prevalence was beyond the main study's scope. Fourth, centers were eligible for inclusion only if they performed an average of ≥ 10 HTx procedures annually. Smaller centers might organize post-HTx care differently, possibly resulting in different MNA prevalence. Finally, timing and, hence, overall implementation NA could not be measured for co-medications, meaning no direct comparison with immunosuppressants was possible across all MNA dimensions.

To summarize, our findings of significantly higher non-adherence to co-medications than to immunosuppressants call both for further investigation of the reasons behind this differential adherence and for the integration of adherence assessment and enhancement interventions for all medications in post-HTx care.

Authorship

All authors listed qualify for authorship based on the recommendations of the International Committee of Medical Journal Editors (ICMJE). Samira Scalco de Almeida wrote the first draft of the manuscript. Remon Helmy worked further on the manuscript and the analysis. The manuscript was fine-tuned with the support of the co-authors. This paper has dual first authorship.

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Conflict of interest statement

None

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Chapter 6

Practice patterns to improve pre- and post-transplant medication adherence in heart transplant centres: A secondary data analysis of the international BRIGHT study

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Practice patterns to improve pre- and post-transplant medication adherence in heart transplant centres: A secondary data analysis of the international BRIGHT study

Abstract

Background: As medication non-adherence is a major risk factor for poor post-transplant outcomes, we explored how adherence is assessed, enhanced and integrated across the transplant continuum.

Aim: The aim of this study was to study practice patterns regarding pre- and post-transplant medication adherence assessment and interventions in international heart transplant centres.

Methods: We used data from the Building Research Initiative Group: chronic illness management and adherence in heart transplantation (BRIGHT) study, a cross-sectional study conducted in 36 heart transplant centres in 11 countries. On a 27-item questionnaire, 100 clinicians (range one to five per centre) reported their practice patterns regarding adherence assessment and intervention strategies pre-transplant, immediately post-transplant, less than one year, and one or more year post-transplant. Educational/cognitive, counselling/behavioural and psychosocial/affective strategies were assessed. Clinicians' responses (intervention present vs. absent; or incongruence in reporting intervention) were aggregated at the centre level.

Results: The adherence assessment method most commonly used along the transplant continuum was questioning patients (range 75–88.9%). Pre-transplant, all three categories of intervention strategy were applied. Providing reading materials (82.9%) or instructions (68.6%), involving family or support persons in education (91.4%), and establishing partnership (91.4%) were used most frequently. Post-transplant, strategies closely resembled those employed pre-transplant. Training patients (during recovery) and cueing were more often applied during hospitalisation (74.3%). After the first year post-transplant, except for motivational interviewing (25.7–28.6%), the number of strategies decreased.

Conclusions: Across the transplant continuum, diverse adherence interventions are implemented; however, post-transplant, the frequency of adherence interventions decreases. Therefore, increased investment is necessary in long-term adherence interventions.

Introduction

Medication adherence is crucial to successful long-term outcomes after transplantation (Tx).(1,2) Defined as '[the] process by which patients take their medication as prescribed', medication adherence involves three components: initiation, implementation, and discontinuation.(3) Medication non-adherence may involve late or non-initiation of the prescribed regimen, suboptimal implementation of the treatment (not taking medications; drug holidays; wrong timing; dose reduction), and early discontinuation of treatment.

Independent of the assessment method and operational definition used, the magnitude of medication non-adherence in heart Tx recipients is high. Using meta-analytical techniques, Dew et al.(4) reported a non-adherence rate of 14.5 cases per 100 patients per year. The Swiss Transplant Cohort Study, which assessed medication non-adherence along the transplant continuum in solid organ recipients, recorded self-reported non-adherence rates ranging from 7.9% pre-Tx to 18.8% three years post-Tx in their heart Tx group.(5) Post-heart Tx, the self-reported non-adherence rate to co-medications was 39.2%.(6)

In end-stage heart disease, as well as after heart Tx, medication non-adherence is associated with poor clinical(1,2,7–9) and economic outcomes.(10) In addition, in heart Tx even minimal deviations from the prescribed dosing schedule have been linked with poor outcomes.(1,2)

Given the serious risks of medication non-adherence and the limited forgiveness of immunosuppressive regimens, guidelines for heart Tx therefore indicate a need to integrate medication adherence assessment and interventions into routine transplant care.(11) However, no evidence is currently available as to how international practice guidelines are implemented along the heart Tx care continuum. Using a methodological approach similar to those used in cardiovascular care(12) and after solid organ(13) or stem cell Tx,(14) our research group cross-sectionally assessed post-transplant medication adherence in relation to practice patterns in heart Tx centres. In addition to mapping the adherence assessment methods used (e.g. direct observation, blood assay results and indirect measures (self-report, collateral report, pill count, prescription refill, electronic monitoring)), we noted whether the intervention strategies used to improve medication adherence were educational/cognitive, counselling/behavioural, or psychosocial/affective.(15)

De Bleser et al.(15) defined these three intervention categories as follows: educational/cognitive interventions convey information verbally, in writing, and/or audiovisually, either individually or in group settings; counselling/behavioural interventions shape and/or reinforce target behaviours, support patients to participate actively in their own

care, increase their skill levels or improve their routines; psychosocial/affective interventions act on patients' feelings, emotions and social support. We refer to combinations of these categories as mixed interventions. Previous medication adherence practice pattern studies(12–14, 16) showed that, regarding adherence-enhancing intervention strategies, clinicians applied mostly educational/cognitive strategies.

Given the scarcity of related international evidence, the objective of this study was to describe international practice patterns regarding medication adherence assessment methods and intervention strategies across the transplantation continuum among heart Tx centres. Data were collected first pre-transplant, then at three post-Tx measurement points, (i.e. during hospitalisation post-Tx surgery, less than one year, and one or more year post-transplant).

Methods

Design, setting and sample

The present study's design is a secondary analysis using data from the Building Research Initiative Group: chronic illness management and adherence in transplantation (BRIGHT) study,(17) an 11-country multicentre, cross-sectional study including 36 heart Tx centres. The investigation conforms with the principles outlined in the Declaration of Helsinki.(18) The BRIGHT study's goal was to assess variability related to various health behaviours among heart transplant patients internationally, to assess multilevel risk factors for medication non-adherence and to map and compare practice patterns among heart Tx centres with regard to chronic illness management. Therefore the BRIGHT study used different questionnaires (BRIGHT patient self-report questionnaire, BRIGHT patient interview questionnaire, BRIGHT clinicians' self-report questionnaire, BRIGHT heart transplant director questionnaire and BRIGHT medical data extraction sheet) to assess the variables of interest. This substudy uses data collected through the BRIGHT clinicians' self-report questionnaire in which practice patterns regarding adherence assessment and adherence intervention strategies were assessed among other variables.

Data were collected from March 2012 to October 2015. Details of the BRIGHT study's methodology have been reported elsewhere.(17) Using a multistage sampling approach, the BRIGHT study included a convenience sample of 11 countries (Belgium, France, Germany, Italy, Spain, Switzerland, UK, Australia, Canada, USA and Brazil), a convenience sample of 36 heart Tx centres (minimum two centres per country) and 100 clinicians practising in these heart Tx centres (one to five per centre). Inclusion criteria for heart Tx centres were the following: 50 or more heart Tx performed in the one to five years prior to inclusion, a location in one of the selected countries, and a formal letter of support signed by the centre's transplant director and responsible administrator. The eligibility criteria for clinicians were the following:

over six months' experience in their heart Tx centre; employment of 50% or greater in direct clinical practice; and familiarity with their centre's post-Tx outpatient care. In cases when, based on these selection criteria, more than five clinicians were available, five were selected using a random sampling procedure. When fewer than five were available, all eligible clinicians were included. The BRIGHT study was approved by every participating transplant centre's local ethics committee.

Variables and measurement

Characteristics of the heart transplant centres were reported by the transplant directors, using an investigator-developed instrument. The following variables were reported: type of centre (university teaching hospital, regional or community hospital, other); total number of heart Tx performed at the centre in the 12 months prior to enrolment in the BRIGHT study (2011); mean length of inpatient stay (in days) immediately after heart Tx; and total number of included heart Tx recipients in follow-up at the first data collection point more than one year post-Tx.

Demographics of clinicians were provided directly by the clinicians, including information on nine variables: age in years; gender; current position in an heart Tx programme (transplant coordinator, staff nurse, advanced practice nurse, cardiologist); total years practising; years practising in heart Tx; years practising in current heart Tx programme; percentage of work spent in heart Tx care; primary workplace area (inpatient Tx unit, outpatient Tx unit, inpatient, and outpatient Tx unit); and completion of a certification programme in transplantation care (yes/no).

Practice patterns with regard to adherence assessment and adherence intervention strategies were assessed via a questionnaire developed by Berben et al.(12) and completed by the participating transplant clinicians. This questionnaire was developed based on state-of-the-art literature.(19–23) Content validity had been established in a group of expert clinicians working in organ Tx centres in the USA and the UK.(12) The questionnaire has already been used in different transplant populations.(12–14) Medication adherence was assessed using three methods: (a) questioning patients about medication adherence; (b) screening patients for risk factors for non-adherence (e.g. forgetfulness, busy lifestyle, complex treatment, etc.); and (c) using an electronic monitoring device to assess medication adherence. Furthermore, the questionnaire included a total of 24 items to assess adherence-enhancing interventions implemented and used in daily transplant practice (yes/no) at four time points along the transplant continuum: pre-Tx; during hospitalisation following transplant surgery; less than one year post-Tx; and one or more year post-Tx. Six items assessed educational/cognitive interventions; 10 measured counselling/behavioural interventions; and eight assessed

psychosocial/affective interventions. Clinicians were asked to indicate (yes/no) which of the adherence assessment methods and strategies their Tx programmes used.

As several clinicians per centre could report on practice patterns, we aggregated the clinicians' information at the transplant centre level. We scored an assessment or intervention as 'present' if all clinicians from one centre congruently responded 'yes' on the associated item. In cases in which all clinicians reported that an intervention was not used in their transplant centre, we scored this item as 'absent'. When incongruences occurred between clinicians' responses, we scored 'incongruence in reporting intervention'.

Data analysis

We used descriptive statistics (frequencies, percentages, means/standard deviations and medians/interquartile ranges (IQRs)) as appropriate, based on measurement levels and distributions, to describe centre and clinician characteristics. Aggregated practice pattern data were summarised at the centre level for the three answer categories (present, absent, or incongruence in reporting intervention).

As fewer than 10% of responses were missing, no data imputation was performed. Missing responses per category are reported in **figures 6.1–6.5**. Statistical analyses were performed using SPSS 23 (IBM SPSS Inc., Armonk, NY, USA).

Results

Sample characteristics

Characteristics of participating Tx centres and transplant clinicians are shown in **tables 6.1 and 6.2**, respectively. A median of 20.0 (IQR 18.0, range 4–87) transplant procedures were performed per year, with a median of 325 (IQR 289.5, range 27–1500) heart Tx recipients with a post-transplant status of more than one year in follow-up in the respective heart Tx centre (**table 6.1**). Most clinicians (N=87, 87.0%) were women, with a mean age of 45.9 years (SD 10.2); their most common position title was transplant coordinator (n=42, 42.0%) (**table 6.2**).

Table 6.1: Characteristics of participating heart transplant centres

Variable	N = 36
Type of a transplant centre, n (%)	
University teaching hospital	30 (83.3)
Regional or community hospital	4 (11.1)
Other ^a	2 (5.6)
Total number of heart transplantations performed at a centre during past year (in 2011) ¹	
Median (IQR)	20.0 (18.0)
Range	4 - 87
Length of stay after a heart transplant in the hospital at a centre (in days)	
Median (IQR)	21.0 (10.7)
Range	9- 38
Total number of heart transplant recipients > 1 year post-transplant in follow-up ²	
Median (IQR)	325 (289.5)
Range	27- 1500

¹ missing n=2, ²missing n=2; IQR: interquartile range; SD: standard deviation

^aOther types of centres including: one private & teaching non- profit hospital, one philanthropic institution

Table 6.2: Clinicians' characteristics

Variable	N = 100
<i>Age (years) ¹</i>	
Mean ± SD	45.9 ± 10.2
<i>Gender, n (%)</i>	
Female	87 (87.0)
<i>Current position in a transplant program, n (%)</i>	
Transplant Coordinator	42 (42.0)
Staff nurse	39 (39.0)
Advanced Practice Nurse	16 (16.0)
Cardiologist	3 (3.0)
<i>Years practicing</i>	
Median (IQR)	22.0 (18.0)
<i>Years practicing in heart transplantation²</i>	
Median (IQR)	11.0 (13.0)
<i>Years practicing in the a current heart transplant program³</i>	
Median (IQR)	8.0 (10.0)
<i>Percentage of work in heart transplant care⁴</i>	
Mean ± SD	81.0 ± 26.9
Median (IQR)	100 (50.0)
Range	10- 100
<i>Primary workplace, n (%)</i>	
Outpatient transplant unit	48 (48.0)
Inpatient and outpatient transplant unit	37 (37.0)
Inpatient transplant unit	10 (10.0)
Other ^a	5 (5.0)
<i>Certification in transplantation</i>	
Yes, n (%)	15 (15.0)

¹missing n=2; ² missing n=1; ³missing n=2; ⁴missing n=2; IQR: interquartile range; SD: standard deviation

^aPrimary workplaces including: cardiomyopathy unit, outpatient transplant unit and day hospital, critical care unit (ICU)

Practice patterns regarding adherence assessment methods

Figure 6.1 shows practice patterns related to adherence assessment methods. Across the entire transplant continuum, the most commonly used assessment method was questioning patients about medication adherence, with 75% of heart Tx centres using it pre-Tx and 88.9% using it in the first year post-Tx. Screening for risk factors ranged from 69.4% pre-Tx to 83.3% in the first year post-Tx. The least popular assessment method, electronic monitoring, was used by only 2.8% of centres, and only in the first year post-Tx.

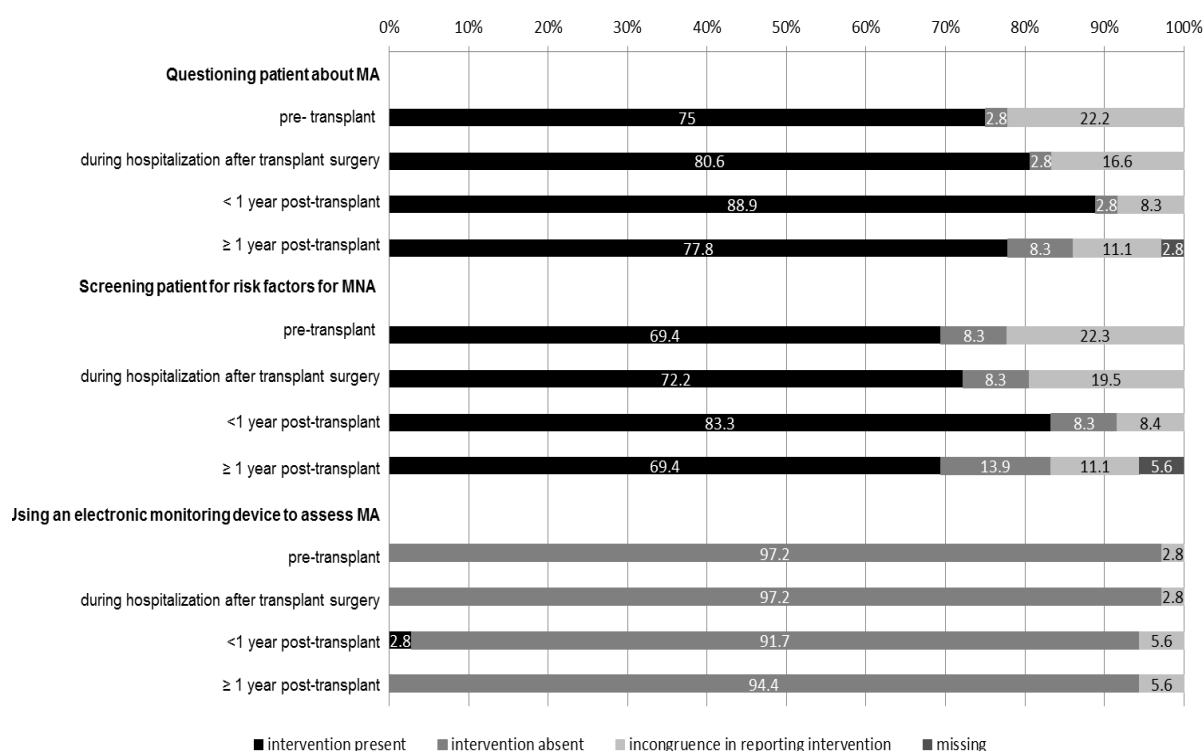


Figure 6.1: Adherence assessment methods used at 4 time periods from pre- to > 1 year post-transplant (N=36)

MA = medication adherence, MNA = medication non-adherence

Practice patterns regarding adherence intervention strategies

All three types of the assessed intervention strategies (educational/cognitive, counselling/behavioural and psychosocial/affective) were applied to varying degrees both pre and post-transplant. The numbers and types of strategies applied varied considerably both between centres and across time periods (**figures 6.2 - 6.5**).

Pre-transplant practice patterns, involving family or support persons in education and establishing partnerships with patients and their significant others, were used in 91.4% of transplant centres, followed by providing reading materials (82.9%), providing individual

instruction (77.1%) and providing instruction regarding medication intake (68.6%) (**figure 6.2**). Counselling–behavioural strategies were less frequently used pre-Tx. For this period, the most commonly applied strategy was training patients regarding medication intake (57.1%) (**figure 6.2**).

Post-transplant practice patterns mainly resembled those reported pre-transplant. The only exception was training patients regarding medication intake during inpatient recovery, which was used by 100% of the included centres (**figures 6.2 and 6.5**). Still, adherence reminders during clinical visits (a counselling/behavioural strategy) were used more frequently post-transplant (67.6–74.3%) (**figure 6.4**) than pre-transplant (57.1%) (**figure 6.2**).

Use of computer-assisted educational programmes varied from 8.3% (pre-Tx and during hospitalisation after transplant surgery) to 2.9% (during the first year post-Tx). While video tutorials were the most used educational/cognitive intervention pre-transplant (17.1%), fewer than 5% of centres reported using them at other post-transplant time points (2.9–8.3%) (**figures 6.2 and 6.3**). Across the Tx continuum, the use of electronic monitoring devices was rare (2.9–5.7%) (**figures 6.2 and 6.4**).

Importantly, examining the evolution of the most commonly applied strategies over time, decreases were observed in most interventions beyond the first year post-transplant (**figures 6.3–6.5**). There were three exceptions: reducing the complexity of the medication regimen (which rose from 45.7% to 57.1%) (**figures 6.2 and 6.4**), using motivational interviewing (which increased slightly from 25.7% to 28.6%) (**figure 6.5**) and establishing case management services (which remained stable at 22.9%) (**figure 6.5**).

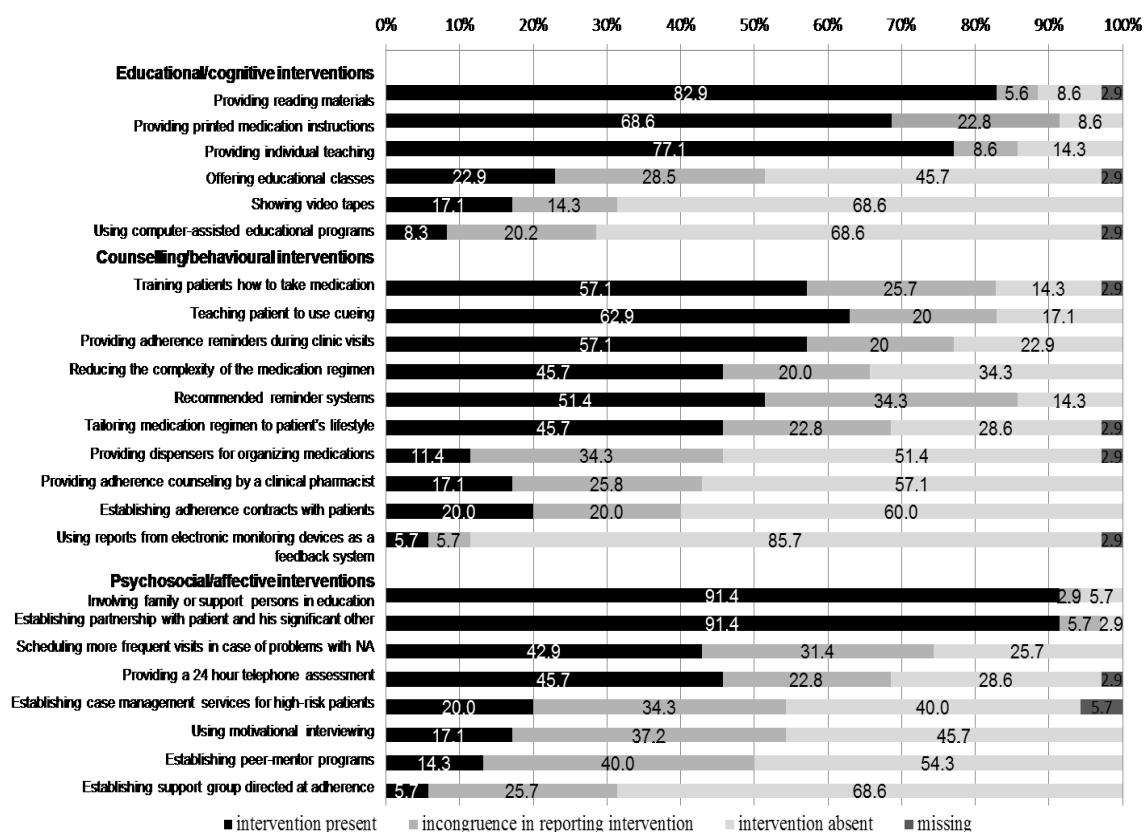


Figure 6.2: Percentages of applied medication adherence intervention strategies in heart transplant centres pre-transplant (N=36)

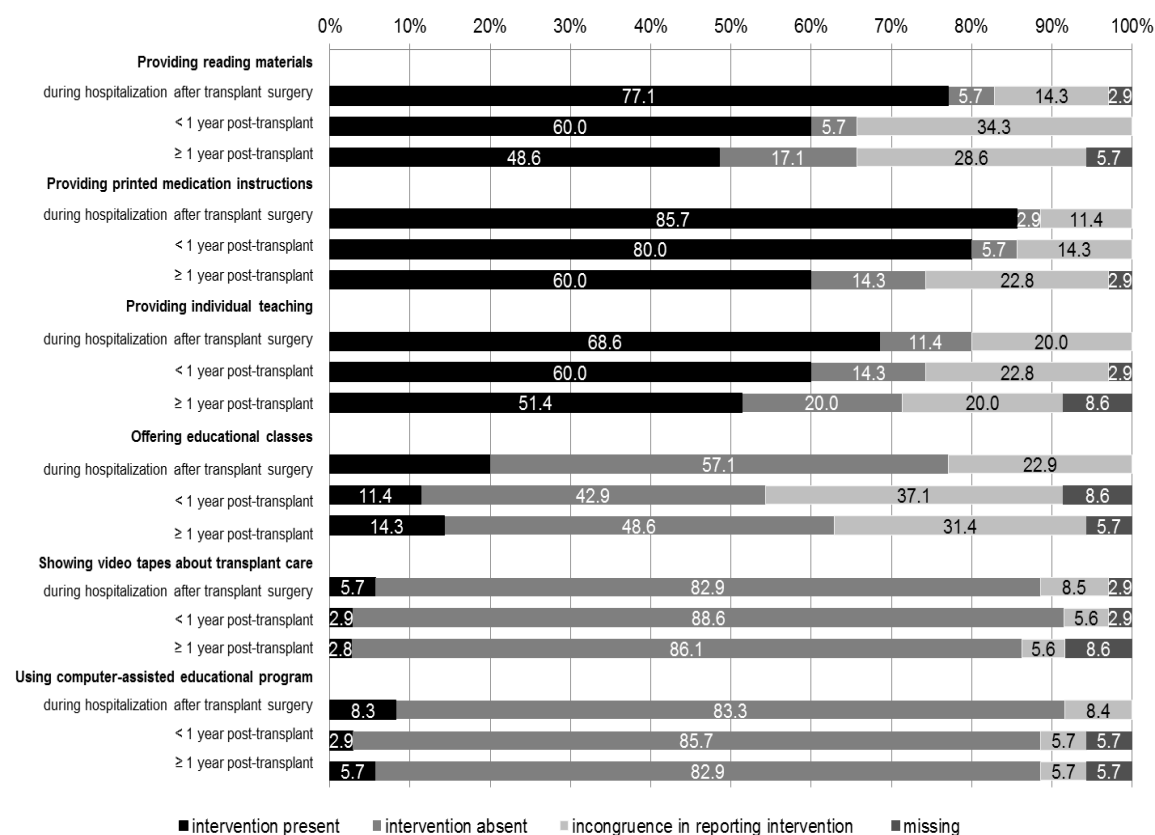


Figure 6.3: Percentages of educational/cognitive intervention strategies in heart transplant centres post-transplant (N=36)

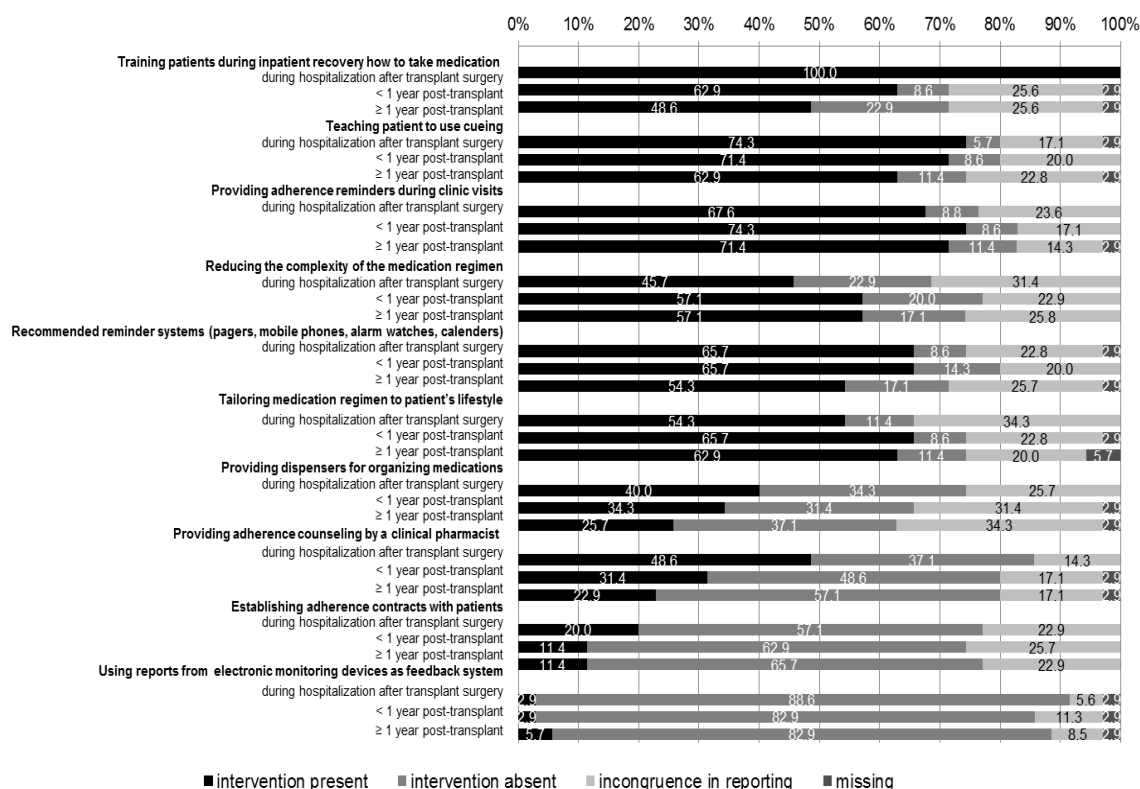


Figure 6.4: Percentages of applied counselling/behavioural intervention in heart transplant centres post-transplant (N=36)

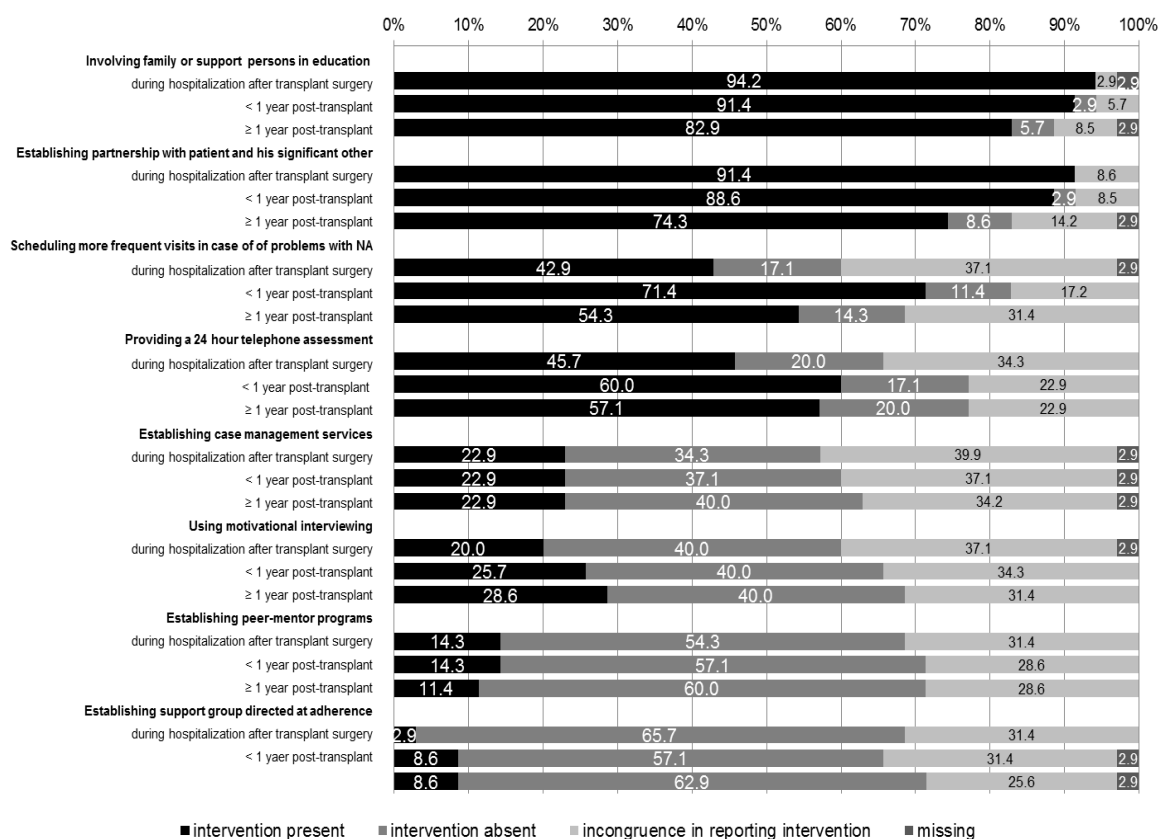


Figure 6.5: Percentages of applied psychosocial/affective intervention strategies in heart transplant centers post-transplant (N=36)

Discussion

The International Society for Heart and Lung Transplantation (ISHLT) consensus statement⁽¹¹⁾ calls for the integration of adherence assessment and management into heart transplant care. Using a sample of 36 heart transplant centres in 11 countries on four continents, the present study is the first to provide such extensive information on practice patterns of medication adherence assessment and medication adherence strategies along the transplant continuum. To our knowledge, its data source, the BRIGHT study, is the largest ever systematically to map practice patterns regarding adherence assessment and interventions in solid organ transplantation⁽¹³⁾ as well as in other chronic diseases.^(24, 25) Our findings highlight the fact that, with some variability between intervention types and phases, a growing number of transplant centres have integrated medication adherence assessment and interventions into regular care along the transplant continuum. Compared to earlier studies addressing healthcare professionals working in different transplant programmes,^(12, 13, 26) we observed a trend in more implemented adherence-enhancing interventions. ISHLT guidelines and increased awareness of the importance of medication adherence in transplantation very likely encouraged investment in assessing this risk factor for poor post-Tx outcomes.⁽¹¹⁾

According to our findings, questioning patients about medication adherence via self-report was the most commonly applied assessment method. This finding is similar to those of earlier European studies in cardiovascular⁽¹²⁾ and transplant patients.^(13, 14) In clinical practice, patient self-report is an easily implemented approach that allows quick, economical assessment of medication adherence.⁽²⁷⁾ However, used alone, self-reporting commonly underestimates patients' non-adherence;⁽²⁷⁾ therefore, to increase its sensitivity, a combination of assessment strategies is recommended.⁽²⁸⁾ Furthermore, in line with a recent Institute of Medicine report regarding the handling of psychosocial and behavioural data, adherence information should also be integrated into the patient's electronic medical record.⁽²⁹⁾

Although the significance of non-adherence to immunosuppressive medication has been acknowledged by the healthcare transplant community for many years, our data indicate that few adherence interventions are applied consistently. Many more are used mainly during specific phases of the transplant continuum.⁽¹⁶⁾ Contradicting previous smaller studies applying the same methodology after solid organ transplantation,⁽¹³⁾ after stem cell transplantation,⁽¹⁴⁾ and in cardiovascular care,⁽¹²⁾ we found that the prevalence of educational/cognitive interventions (e.g. providing self-care reading materials, printed medication instructions, or individual teaching) has declined. Current findings show the use of more varied adherence interventions in heart transplant care, the most common of which

use counselling/behavioural strategies, e.g. training patients during their inpatient recovery to take their medications properly at home, or teaching patients to use cueing. Psychosocial/affective strategies (e.g. involving family or other support persons in educational and behavioural interventions, others) are also integrated, but to a lesser extent.

Still, while certain adherence-enhancing strategies are clearly more effective than others, the most useful are not the most frequently used. Meta-analyses and systematic reviews focusing on the efficacy of adherence-enhancing interventions indicate that succinct written instructions, packaging interventions, electronic reminders (e.g. via text messaging), and simplification of the medication regimen are most efficacious to improve patients' long-term medication adherence.(30, 31) Recently published randomised controlled studies in transplantation also highlight the value of electronic monitoring feedback(32) and behavioural contracts.(33) However, the most recent meta-analysis examining the efficacy of adherence-enhancing intervention strategies suggests that complex interventions involving multiple components tailored towards the patient's needs improve medication adherence most effectively.(34) This necessitates a comprehensive assessment of patients' needs and potential barriers against an optimal medication adherence. Further research is needed to demonstrate whether the same strategies are also effective to maintain medication adherence.

One key finding of our study is the observed decrease in the intensity of adherence interventions from the first year post-Tx to more than one year post-Tx. Given the reported correlation between increases in medication non-adherence and elapsed time post-transplant,(5) this is particularly worrisome. The call for continuous life-long support of medication adherence might also be underlined by the recent findings of a qualitative interview study in 14 heart transplant recipients. The study clearly illustrated that uncertainty can be seen as a common state among heart transplant recipients. Many patients struggle to reorganise their self-structure and everyday life.(35)

Continuous support can be delivered during clinical encounters; but to bridge the gaps between transplant centre visits, E-health approaches could also be used to maintain patient motivation through feedback and reminders.(36–38) However, our data indicate that, compared to direct patient contact, these strategies receive limited use as alternative delivery modes for adherence interventions. Our findings show that, in our sample, the adoption of more sophisticated methods (electronic monitoring, computer assisted learning, video) is limited.

One barrier against integrating medication adherence interventions into clinical practice can be inadequate time and funding in clinical settings throughout the patient's transplant journey.(19) For example, most healthcare systems do not reimburse patient

counselling as a part of the fee for service or capitation payment systems.(19) However, various capitation payment systems cover at least one year of care or outcome-related treatment, offering incentives for effective self-management support. Having proved effective, these systems provide guidance towards successful implementation and sustainability of adherence interventions in clinical practice.(39) Still, transplant clinicians need specific training to assess adherence and intervene when needed.(19) Current best clinical practice also includes chronic care models based on supporting patients' self-management involving collaborative approaches between informed, activated patients and prepared, proactive healthcare teams.(40) Besides self-management support, this model focuses on continuity of care, partnership with families, decision-making support and the use of an elaborative clinical information system. Within this model, the healthcare provider is linked with community resources and policies, as well as the healthcare system. Research on the chronic care model has shown that the chronically ill, e.g. with asthma, have demonstrated improvement in medication adherence.(41)

Limitations

In assessing each centre's practice patterns, we used clinician reports alone, i.e. no independent observations were executed to confirm that those reports reflected actual practice. Nevertheless, given the broad geographical coverage of the BRIGHT study's data collection, no alternative approach was available to map practice patterns. While using various informants from each transplant centre, then combining the information later at the level of the centre is a strength, considerable incongruences were observed between answering patterns (range 5.6–40%). Therefore, we adopted a conservative approach in our analysis, reporting only interventions reported congruently as present.

Also, continent or country-specific analyses were beyond the scope of this study. For future research, then, it might be useful to focus on potential geographical variations in practice patterns related to medication adherence assessment and strategies.

While the use of an established instrument to assess practice patterns regarding applied assessment and intervention strategies allows comparison with previous research, this also has its limitations. Our categorisation of adherence strategies built on our group's previous work assessing educational/cognitive, counselling/behavioural and psychosocial/affective strategies. Given the recent publication of the behaviour change technique taxonomy V1 of Michie et al.,(42) it would be useful to invest in instrument development to assess practice patterns congruent with this taxonomy.

Like the taxonomy of Michie et al., our instrument includes only patient-level interventions. Further, given recent BRIGHT study insights that multilevel factors contribute to Tx medication non-adherence, calling for multilevel interventions – assessment of higher level interventions via an updated instrument (e.g. support systems for drug costs) is recommended.(43, 44) Also, it would be worthwhile to explore further the use of E- health applications in Tx adherence management. Here, patients' individual factors should be considered, as they can influence the efficacy of adherence-enhancing interventions. For example, health literacy is a relevant factor to consider when rolling out adherence interventions.(45) Furthermore, future studies should aim at identifying underlying reasons that are responsible for existing gender differences in patient outcomes. As the recently published NEW HEART study (2017) has shown that women are more likely to experience moderate or severe allograft rejection and to be hospitalised for acute rejection than men, gender aspects should be carefully examined in ongoing cardiovascular adherence research.(46)

Conclusion

Various educational/cognitive, counselling/behavioural and psychosocial/affective adherence-enhancing intervention strategies are implemented along the transplant continuum. However, although non-adherence is known to increase with time, we demonstrated that the application of adherence interventions decreases in the longer term post-transplant. Transplant follow-up care should integrate support for adherence beyond the first year post-transplant when the risk of non-adherence is increasing.

Implications for practice

- Contrary to the current practice of many transplant centres, adherence assessment and intervention strategies should be implemented across the entire transplantation continuum, and not only early after transplantation, as it is known that non-adherence continues to increase over time post-transplant.
- Recent systematic literature reviews and meta-analyses indicate the value of tailored multi-component adherence interventions (e.g. electronic monitoring feedback, behavioural contracts, succinct written instructions, packaging interventions, technically based reminders and simplification of medication regimens).
- E-health technologies are rarely implemented in heart transplant centres, although they can be used to deliver adherence interventions, especially to circumvent the lack of resources to organise long-term follow up.
- Clinicians should be trained to provide sustainable adherence assessment and intervention strategies across the entire transplantation continuum to prevent non-

adherence long-term post-transplant (e.g. methods of strengthening self-management of patients). In particular, training should include the facilitation of new health technologies.

- Providing self-management support in the clinical setting should be strongly backed in the healthcare system through adequate time resources and funding.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Ethical considerations

The BRIGHT study obtained ethical approval from each participating centre's institutional review board/ethics committee prior to data collection. Clinicians' completion of the questionnaire implied voluntary consent to participate in the study. This study does not need separate ethical approval.

Appendix

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Chapter

7

The international prevalence and variability of nonadherence to the nonpharmacologic treatment regimen after heart transplantation: Findings from the cross-sectional BRIGHT study

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The international prevalence and variability of nonadherence to the nonpharmacologic treatment regimen after heart transplantation: findings from the cross-sectional BRIGHT study

Abstract

Introduction: Heart transplant (HTx) recipients need to follow a complex therapeutic regimen. We assessed the international prevalence and variability in non-adherence to six non-pharmacologic treatment components (physical activity, sun protection, diet, alcohol use, non-smoking, and outpatient follow-up visits).

Methods: We used self-report data of 1397 adult HTx recipients from the 36-HTx-center, 11-country, 4-continent, cross-sectional BRIGHT study (ClinicalTrials.gov ID: NCT01608477). The non-adherence definitions used were: Physical activity: <3 times/week 20 minutes' vigorous activity, <5 times/week 30 minutes' moderate activity, or <5 times/week a combination of either intensity; Sun protection: not "always" applying any sun protection; Diet: not "often" or "always" following recommended diet(s); Alcohol use: > 1 alcoholic drink/day (women) or > 2 drinks/day (men); Smoking: current smokers or stopped <1 year before; Follow-up visits: missing ≥ 1 of the last 5 outpatient follow-up visits. Overall prevalence figures were adjusted to avoid over- or underrepresentation of countries. Between-country variability was assessed within each treatment component via chi-square testing.

Results: The adjusted study-wide non-adherence prevalence figures were: 47.8% for physical activity (95% CI [45.2-50.5%]), 39.9% for sun protection (95% CI [37.3-42.5%]), 38.2% for diet recommendations (95% CI [35.1-41.3%]), 22.9% for alcohol consumption (95% CI [20.8%-25.1%]), 7.4% for smoking cessation (95% CI [6.1%-8.7%]), and 5.7% for follow-up visits (95% CI [4.6-6.9%]). Significant variability was observed between countries in all treatment components except follow-up visits.

Conclusion: Non-adherence to the post-HTx non-pharmacologic treatment regimen is prevalent and shows significant variability internationally, suggesting a need for tailored adherence-enhancing interventions.

Introduction

Evidence shows that long-term graft attrition rates after adult heart transplantation (HTx) have not changed markedly over time, and that reduced mortality rates are almost exclusively attributable to survival gains in the early post-HTx phase (1, 2). Improving long-term survival is therefore a priority in research and clinical practice. Nevertheless, immunosuppressant intake might hamper long-term survival (3). Indeed, long-term immunosuppressant intake may trigger systemic and metabolic complications and elevate the risk of cancer, augmenting the risk of graft injury and all-cause mortality. According to the most recent registry data (4), at 5 years post-HTx, 51.1% of HTx recipients have renal dysfunction, 35.5% have diabetes, 29.3% have cardiac allograft vasculopathy, and 15.9% have malignancy (all types combined).

To prevent or delay the incidence of these co-morbidities, post-HTx care guidelines (5) recommend lifelong follow-up to monitor graft function and lifestyle modifications including weight control, physical activity, diet (e.g., low fat and sodium intake), abstinence from smoking or heavy alcohol intake, and use of sun protection. It remains unclear, however, to what extent HTx recipients are able to follow this complex therapeutic regimen. The bulk of evidence on post-HTx behavior focuses on medication adherence; robust evidence on the prevalence of non-adherence to the post-HTx non-pharmacologic therapeutic regimen is scarce.

A 2007 meta-analysis (6) showed non-adherence rates of 33.7 cases per 100 patient-years for physical activity, 28.1 cases for following a diet, 8.5 cases for attending clinic appointments, 4.9 cases for alcohol use, and 3.2 cases for tobacco use in HTx recipients. However, these estimates were based on a small number of available studies. Moreover, although meta-analyses pool and summarize evidence, non-adherence prevalence rates for each behavior might vary widely across studies due to methodological issues, e.g., non-standard measurement methods or sampling strategies. Since that 2007 meta-analysis, the few related studies published have most commonly used small samples or focused on a single behavior. Larger studies investigating multiple behaviors enrolled patients from one center only (6, 7), providing no evidence on variations in HTx recipients' health behaviors between centers or countries. Physical inactivity in the general population, for instance, is far more prevalent in Belgium, Spain and the UK than in the Netherlands, Germany or France (8), and tobacco smoking is more prevalent in Europe than in the Americas (9). Generating and comparing regional non-adherence rates could help HTx centers prioritize lifestyle interventions and plan resources to remedy problems specific to their local populations. Therefore, the international HTx community would benefit from a single large study using a homogeneous methodological approach to investigate the prevalence of non-adherence to all post-HTx non-pharmacologic treatment components.

Therefore, this study has two aims: (1) to describe the prevalence of non-adherence to the post-HTx non-pharmacologic treatment regimen (i.e. physical activity, sun protection, diet recommendations, limiting alcohol use, smoking abstinence, and appointment keeping); and (2) to describe between-country variability in non-adherence rates regarding these health behaviors and test its significance in a large sample of adult HTx recipients from various countries.

Patients and methods

This study used data from the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study (10, 11) (ClinicalTrials.gov ID: NCT01608477), a cross-sectional study assessing healthcare providers' practice patterns and the prevalence and variability of non-adherence to the post-HTx treatment regimen in 36 HTx centers from 11 countries in Asia, Europe, North and South America.

Sampling and data collection

The BRIGHT study used a multistage sampling approach. Countries and HTx centers were included via convenience sampling, enrolling at least 2 centers per country. HTx centers were eligible to participate in the study if they met all of the following criteria:

1. performance of at least 50 HTx over the 60 months prior to inclusion
2. location in Europe, North America, South America, or Australia
3. willingness to provide formal study support through the center's HTx director and responsible administrator.

Using a stratified random sampling approach based on center size (10), HTx recipients were eligible to participate if they:

1. were adults (≥ 18 years at time of enrolment);
2. were transplanted and followed up for routine care at a participating HTx center;
3. received their HTx as a single-organ transplant;
4. underwent a first-time HTx (no re-transplantation);
5. were 1–5 years post-HTx;
6. were able to read and understand one of the study languages; and
7. were willing to provide written informed consent.

HTx recipients were excluded if they had participated in adherence intervention research or drug trials during the 6 months prior to inclusion or if they had received professional support for medication intake. Detailed information on the methodology of the BRIGHT study is reported elsewhere (10, 11).

The data were collected (once for each HTx recipient) between March 2012 and October 2015 after obtaining ethical approval from each participating center's institutional review board (IRB) or ethics committee.

Variables and measurement

To describe the sample, socio-demographic characteristics were collected via patient interviews during a scheduled clinic visit (i.e., age, gender, marital status, ethnicity, educational level, employment status). Clinical data (date of HTx and heart failure etiology) were captured based on chart reviews.

Non-adherence to 6 components of the non-pharmacologic treatment regimen (i.e., physical activity, non-smoking status, limited alcohol use, use of sun protection measures, following of diet recommendations, and the keeping of follow-up appointments) was assessed by a self-report questionnaire during a scheduled outpatient clinic visit (12-16). **Table 7.1** describes how each component was measured and scored.

Table 7.1: Self-report instruments used to measure the investigated health behaviors

Variable	Instrument	<ul style="list-style-type: none"> • Number of items • Recall period • Response options • Non-adherence definitions 	Validity/Reliability
Physical activity (PA)	Brief Physical Activity Assessment tool (12)	<ul style="list-style-type: none"> • 2 items • Average week • No. times/week 20 min. of vigorous PA: <1 time/week / 1-2 times/week / ≥3 times/week & No. times/week 30 min. of moderate PA: <1 time/week / 1-2 times/week / 3-4 times/week / ≥5 time/week • Non-adherence: <3 times/week vigorous PA OR <5 times/week moderate PA OR <5 times/week a combination of either PA intensities 	<p>Assessed against an accelerometer:</p> <p>- criterion validity (10) (κ= 0.40, 95% CI= 0.12-0.69)</p> <p>- inter-rater reliability (10) (κ= 0.53, 95% CI= 0.33-0.72)</p>
Smoking status	1 item from the Swiss Health Survey (13)	<ul style="list-style-type: none"> • 1 item • 1 year • Currently smoking / Stopped smoking less than a year before / Stopped smoking more than a year before / Never smoked • Non-adherent: currently smoking or stopped less than a year before 	No available information on psychometric properties
Alcohol use	Investigator developed (14)	<ul style="list-style-type: none"> • 3 items • Average week • Yes / No; No. shots or glasses/week (1.5 oz. = 45 ml); No. pints of beer/week (1 pint = 12oz. = 355 ml); No. glasses of wine/week (1 glass = 5 oz. = 148 ml) No. times drinking/week: Daily / 3-4 times/week / 1-2 times/month / <1 time/month / Never • Non-adherent = heavy drinker: > 1 drink/day (women); > 2 drinks/day (men) 	No available information on psychometric properties

Variable	Instrument	<ul style="list-style-type: none"> • Number of items • Recall period • Response options • Non-adherence definitions 	Validity/Reliability
Sun protection	Swiss study on health of people with cancer, leukemia, tumor in childhood (15) and Cambridge University Hospitals' perception of skin cancer in transplant recipients scale (16)	<ul style="list-style-type: none"> • 4 items • Current situation • Using sunscreen, wearing protective clothing, staying in the shade, being sensitive to the time of the day: 5-point Likert scale ranging from '1= never' to '5= always' • Non-adherent: not always using at least 1 of these sun protection methods 	Unidimensional scale, having a Cronbach's alpha of 0.59
Diet recommendations	Investigator developed	<ul style="list-style-type: none"> • 5 items • 1 year • Yes/No for advice to follow a specific diet (low salt, low calorie, low saturated fats, low sugar, or other diets) and, correspondingly, a 5-point Likert scale ranging from '1= never' to '5= always' to evaluate adherence to each recommended diet. • Non-adherent: score 1-3 on any of the 5 diets recommended by the transplant team 	No available information on psychometric properties
Follow-up appointment keeping	Investigator developed	<ul style="list-style-type: none"> • 1 item • Previous 5 scheduled clinic appointments • No. appointments missed: 6-point scale ranging from 'none' to '6= all 5 appointments' • Non-adherent: missed ≥ 1 appointment 	No available information on psychometric properties

Statistical analysis

Frequencies and percentages (for categorical variables) or measures of central tendency and dispersion (for continuous variables) are used to describe the sample. The data were aggregated on the country level and the level of the entire sample as appropriate. The prevalence of non-adherence to each of the non-pharmacologic treatment components is presented as a percentage. To avoid over- or underrepresentation of any country's HTx recipient population, the overall non-adherence prevalence for each treatment component was calculated as a weighted average. This was accomplished by multiplying each country's non-adherence rate by a weighting factor that corresponds to the ratio of the HTx recipient population in the corresponding country to that of all included countries in the time period corresponding to that of the study's data collection in the country.

Standard deviations and ranges are used to describe between-country variability in non-adherence prevalence. Chi-square testing was used to determine the significance of this variability. After applying the Bonferroni correction to the significance level of $p < 0.05$ to account for multiple testing, the significance level was set at 0.008.

With one exception—alcohol use—missing data affected fewer than 10% of the cases involving the variables used to calculate non-adherence to the investigated health behaviors. Accordingly, patients with completely missing data on a health behavior of interest were excluded only from the corresponding analysis (available-case analysis). For alcohol use, missing data in the 2 variables, i.e., number of drinks/week and weekly drinking frequency, were imputed using the R (version 3.4.2) programming language and the MICE (Multivariate Imputation by Chained Equations) package. For all other analyses, Stata® 15 (StataCorp LLC, Texas, USA) was used.

Results

Sample characteristics

At the 36 participating centers, of 2523 HTx recipients found eligible for inclusion, 1677 were randomly selected and invited to participate. Of this number, 244 declined and 36 died before enrolment, resulting in a final sample size of 1397 HTx recipients. Information on the sample size per country and health behavior is presented in **table 7.2**.

Table 7.3 shows the main characteristics of the final HTx recipient sample, overall and per country. Participants were 72.7% (1011) male, and on average 53.7 (SD: 13.2) years old and 3.4 (SD: 1.4) years post-HTx at time of enrollment.

Table 7.2: Number of heart transplant recipients with data on each of the investigated behaviors (per country and per health behavior)

	Appointment keeping	Smoking cessation	Alcohol use	Diet recommendations	Sun protection	Physical activity
Belgium (n=74)	74	74	74	48	70	74
France (n=160)	157	157	160	110	150	146
Germany (n=67)	65	64	67	19	62	65
Italy (n=111)	111	110	111	64	110	105
Spain (n=227)	224	221	227	218	220	222
Switzerland (n=47)	46	46	47	14	44	46
United Kingdom (n=99)	99	99	98	28	98	96
Canada (n=121)	116	115	120	88	116	116
USA (n=340)	336	335	339	278	334	334
Australia (n=51)	51	51	51	26	51	51
Brazil (n=100)	97	97	100	71	94	85
Total sample (N=1397)	1376	1369	1394	964*	1349	1340
Missing data	21	28	3	81	48	57

*352 HTx recipients reported not having been recommended any diet

Table 7.3: Sociodemographic and clinical characteristics of the participating heart transplant recipients

	Overall	Europe							North America		Australia	South America
	N=1397	n=785							n=461		n=51	n=100
		Belgium	France	Germany	Italy	Spain	Switzerland	UK	Canada	USA	Australia	Brazil
		n=74	n=160	n=67	n=111	n=227	n=47	n=99	n=121	n=340	n=51	n=100
Age, years (n)	1380	74	160	65	111	227	47	98	113	335	51	99
Mean (SD)	53.7 (13.2)	53.3 (12.6)	50.2 (13.0)	55.3 (10.3)	56.7 (12.5)	56.5 (11.7)	50.1 (14.6)	49.3 (14.8)	55 (13.4)	56.3 (12.8)	49.7 (14.2)	46.8 (13.3)
Gender (n)	1390	74	160	65	111	227	47	98	120	337	51	100
Male, n (%)	1011 (72.7%)	50 (67.6%)	121 (75.6%)	50 (76.9%)	93 (83.8%)	174 (76.7%)	32 (68.1%)	76 (77.6%)	87 (72.5%)	229 (68%)	31 (60.8%)	68 (68%)
Ethnicity (n)	1381	74	159	65	111	224	47	99	119	336	47	100
Caucasian, n (%)	1186 (85.9%)	73 (98.7%)	142 (89.3%)	65 (100%)	110 (99.1%)	205 (91.5%)	43 (91.5%)	93 (93.9%)	106 (89.1%)	251 (74.7%)	33 (70.2%)	65 (65%)
Education (n)	1377	73	158	65	111	220	47	99	119	339	50	96
Primary school, n (%)	187 (13.6%)	3 (4.1%)	10 (6.3%)	7 (10.8%)	37 (33.3%)	94 (42.7%)	5 (10.6%)	0	3 (2.4%)	3 (0.9%)	0	25 (26%)
Secondary school, n (%)	426 (30.9%)	42 (57.5%)	53 (33.5%)	6 (9.2%)	51 (46%)	60 (27.3%)	3 (6.4%)	45 (45.5%)	35 (29.4%)	71 (20.9%)	9 (18%)	51 (53.1%)
Further education, n (%)	294 (21.4%)	15 (20.6%)	64 (40.5%)	40 (61.5%)	2 (1.8%)	25 (11.4%)	32 (68.1%)	24 (24.2)	16 (13.5%)	59 (17.4%)	17 (34%)	0
University, n (%)	470 (34.1%)	13 (17.8%)	31 (19.6%)	12 (18.5%)	21 (18.9%)	41 (18.6%)	7 (14.9%)	30 (30.3%)	65 (54.6%)	206 (60.8%)	24 (48%)	20 (20.8%)
Employment status (n)	1391	74	160	65	111	226	47	99	119	339	51	100
Employed, n (%)	413 (29.7%)	18 (24.3%)	58 (36.3%)	17 (26.2%)	33 (29.7%)	27 (12%)	20 (42.6%)	37 (37.4%)	39 (32.8%)	117 (34.5%)	25 (49%)	22 (22%)
Marital status (n)	1387	74	159	65	110	227	47	97	120	337	51	100
Single, n (%)	242 (17.5%)	8 (10.8%)	36 (22.6%)	8 (12.3%)	14 (12.7%)	26 (11.5%)	8 (17%)	26 (26.8%)	19 (15.8%)	60 (17.8%)	13 (25.5%)	24 (24%)
Married/cohabiting, n (%)	955 (68.9%)	56 (75.7%)	103 (64.8%)	49 (75.4%)	83 (75.5%)	158 (69.6%)	32 (68.1%)	59 (60.8%)	82 (68.3%)	234 (69.4%)	34 (66.7%)	65 (65%)
Divorced/separated, n (%)	149 (10.7%)	8 (10.8%)	19 (12%)	6 (9.2%)	11 (10%)	33 (14.5%)	6 (12.8%)	10 (10.3%)	11 (9.2%)	30 (8.9%)	4 (7.8%)	11 (11%)
Widowed, n (%)	41 (3%)	2 (2.7%)	1 (0.6%)	2 (3.1%)	2 (1.8%)	10 (4.4%)	1 (2.1%)	2 (2.1%)	8 (6.7%)	13 (3.9%)	0	0
Time post-HTx (n)	1395	74	160	67	111	227	47	99	121	340	49	100

	Overall	Europe							North America		Australia	South America
	N=1397	n=785							n=461		n=51	n=100
		Belgium	France	Germany	Italy	Spain	Switzerland	UK	Canada	USA	Australia	Brazil
		n=74	n=160	n=67	n=111	n=227	n=47	n=99	n=121	n=340	n=51	n=100
Years, Mean (SD)	3.4 (1.4)	3.4 (1.2)	3.6 (1.3)	3.4 (1.4)	3.2 (1.3)	3.6 (1.3)	3.5 (1.2)	3.5 (1.2)	3.7 (1.4)	3 (1.3)	4.2 (1.3)	2.8 (1.5)
Heart failure etiology (n)	1362	74	159	65	111	226	47	93	118	328	48	93
Idiopathic	714 (52.4%)	33 (44.6%)	88 (55.4%)	33 (50.8%)	69 (62.2%)	130 (57.5%)	31 (66%)	55 (59.1%)	68 (57.6%)	144 (43.9%)	31 (64.6%)	32 (34.4%)
Ischemic	401 (29.4%)	28 (37.8%)	44 (27.7%)	23 (35.4%)	31 (27.9%)	64 (28.3%)	8 (17%)	18 (19.4%)	35 (29.7%)	128 (39%)	11 (22.9%)	11 (11.8%)
Valvular	44 (3.2%)	2 (2.7%)	10 (6.3%)	0	3 (2.7%)	15 (6.6%)	3 (6.4%)	1 (1.1%)	1 (0.9%)	4 (1.2%)	1 (2.1%)	4 (4.3%)
Congenital	45 (3.3%)	2 (2.7%)	5 (3.1%)	1 (1.5%)	3 (2.7%)	6 (2.7%)	2 (4.3%)	14 (15.1%)	5 (4.2%)	4 (1.2%)	2 (4.2%)	1 (1.1%)
Other	158 (11.6%)	9 (12.2%)	12 (7.6%)	8 (12.3%)	5 (4.5%)	11 (4.9%)	3 (6.4%)	5 (5.4%)	9 (7.7%)	48 (14.6%)	3 (6.3%)	45 (48.4%)

Overall prevalence of non-adherence to the non-pharmacologic treatment regimen

Figure 7.1 shows the overall unadjusted and adjusted prevalence of non-adherence to the different non-pharmacologic treatment components. Based on the adjusted values, the highest prevalence of non-adherence was observed for physical activity: 47.8% (95% CI [45.2%-50.5%]) of the sample were insufficiently physically active. Sun protection followed, with 39.9% (95% CI [37.3%-42.5%]) not always protecting themselves as recommended. Of those who were advised to follow specific diets, 38.2% (95% CI [35.1%-41.3%]) did not always or often follow recommendations. Heavy alcohol use was reported by 22.9% (95% CI [20.8%-25.1%]); 7.4% (95% CI [6.1%-8.7%]) were still smokers or had stopped less than one year prior to data collection. Appointment keeping had the lowest non-adherence prevalence, with 5.7% (95% CI [4.6%-6.9%]) missing at least one of their prior five outpatient clinic appointments.

Between-country variability in non-adherence prevalence

Figure 7.2 shows the between-country variability in the prevalence of non-adherence to each of the investigated health behaviors. The largest variability (SD: 13.6%) was observed in heavy alcohol use, which ranged from 2% in Brazil to 42.9% in the UK. This was followed by variability in non-adherence to sun protection (SD: 9.5%): 24.1% of Spanish HTx recipients did not always use sun protection as opposed to 51.4% in Belgium, which had the highest prevalence. Variability in insufficient physical activity (SD: 8.5%) came third, with Spain's participants having the lowest rate (32%) and France's the highest (59.6%). Diet non-adherence came fourth (SD: 7.1%), varying from 26.6% (Spain) to 48.2% (USA). In Australia, no HTx recipients reported non-adherence to smoking cessation, while this number was 12.7% in France, with relatively low variability between countries (SD: 4%). Non-adherence to appointment keeping had the lowest variability (SD: 2.9%) ranging from 3% (UK) to 11.8% (Australia).

Table 7.4 shows that the observed variability was statistically significant for all behaviors except appointment keeping. **Figure 7.3** depicts each behavior's non-adherence prevalence per country, indicating which behaviors are least and most problematic within each country.

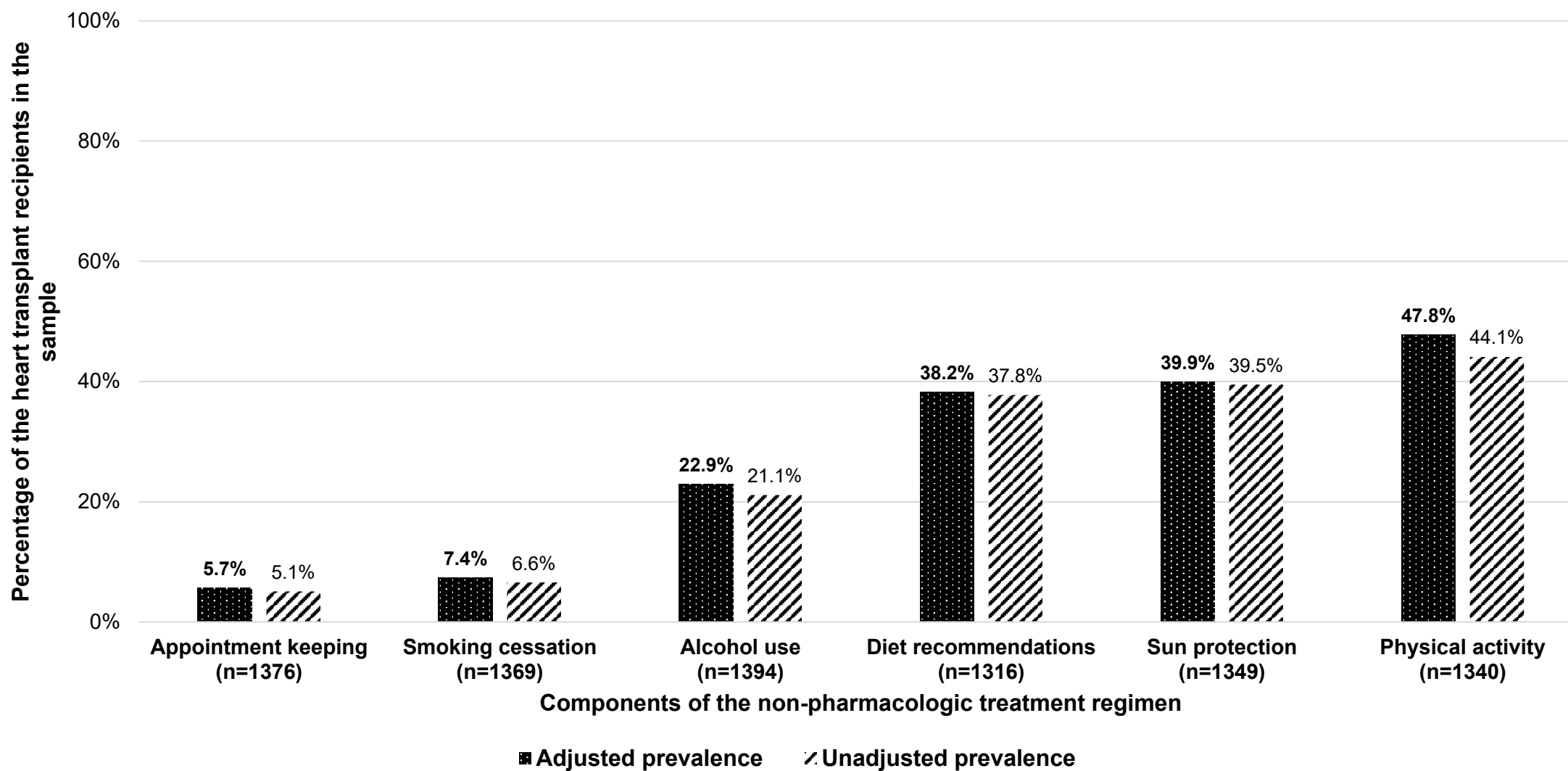


Figure 7.1: The adjusted and unadjusted overall prevalence of non-adherence to the non-pharmacologic treatment regimen

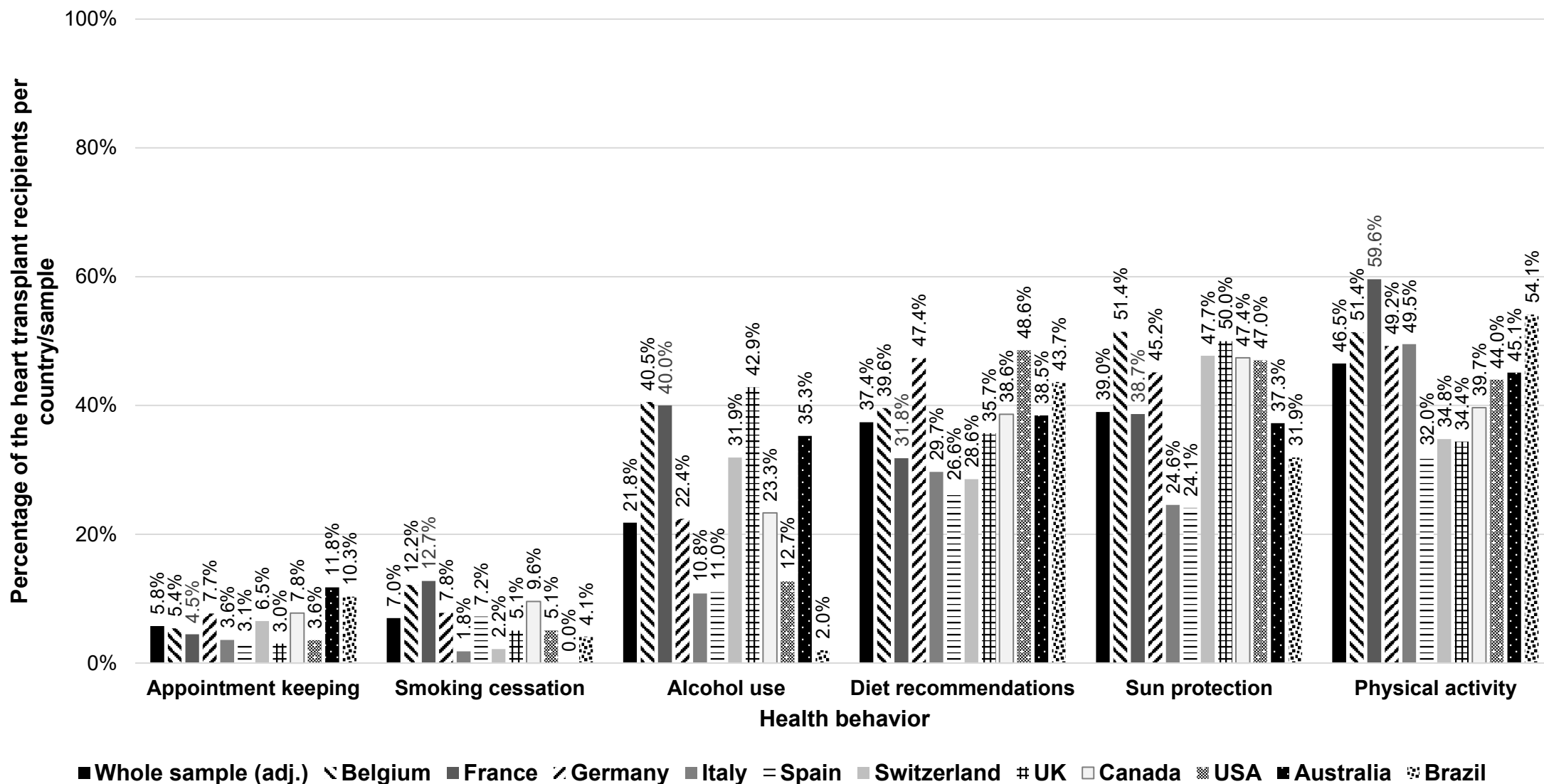


Figure 7.2: Behavior-wise investigation of the variability in non-adherence prevalence between countries

Table 7.4: Chi-square test results for the between-country variability within each health behavior (showing non-adherence rates)

	Appointment keeping		Smoking cessation		Alcohol use		Diet recommendations		Sun protection		Physical activity	
	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent
Belgium	70	4	65	9	44	30	29	19	34	36	36	38
	(94.6%)	(5.4%)	(87.8%)	(12.2%)	(59.5%)	(40.5%)	(60.4%)	(39.6%)	(48.6%)	(51.4%)	(48.6%)	(51.4%)
France	150	7	137	20	96	64	75	35	92	58	59	87
	(95.5%)	(4.5%)	(87.3%)	(12.7%)	(60%)	(40%)	(68.2%)	(31.8%)	(61.3%)	(38.7%)	(40.4%)	(59.6%)
Germany	60	5	59	5	52	15	10	9	34	28	33	32
	(92.3%)	(7.7%)	(92.2%)	(7.8%)	(77.6%)	(22.4%)	(52.6%)	(47.4%)	(54.8%)	(45.2%)	(50.8%)	(49.2%)
Italy	107	4	108	2	99	12	45	19	83	27	53	52
	(96.4%)	(3.6%)	(98.2%)	(1.8%)	(89.2%)	(10.8%)	(70.3%)	(29.7%)	(75.5%)	(24.5%)	(50.5%)	(49.5%)
Spain	217	7	205	16	202	25	160	58	167	53	151	71
	(96.9%)	(3.1%)	(92.8%)	(7.2%)	(89%)	(11%)	(73.4%)	(26.6%)	(75.9%)	(24.1%)	(68%)	(32%)
Switzerland	43	3	45	1	32	15	10	4	23	21	30	16
	(93.5%)	(6.5%)	(97.8%)	(2.2%)	(68.1%)	(31.9%)	(71.4%)	(28.6%)	(52.3%)	(47.7%)	(65.2%)	(34.8%)
United Kingdom	96	3	94	5	56	42	18	10	49	49	63	33
	(97%)	(3%)	(94.9%)	(5.1%)	(57.1%)	(42.9%)	(64.3%)	(35.7%)	(50%)	(50%)	(65.6%)	(34.4%)
Canada	107	9	104	11	92	28	54	34	61	55	70	46
	(92.2%)	(7.8%)	(90.4%)	(9.6%)	(76.7%)	(23.3%)	(61.4%)	(38.6%)	(52.6%)	(47.4%)	(60.3%)	(39.7%)
USA	324	12	318	17	296	43	143	135	177	157	187	147
	(96.4%)	(3.6%)	(94.9%)	(5.1%)	(87.3%)	(12.7%)	(51.4%)	(48.6%)	(53%)	(47%)	(56%)	(44%)

	Appointment keeping		Smoking cessation		Alcohol use		Diet recommendations		Sun protection		Physical activity	
	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent
Australia	45	6	51	0	33	18	16	10	32	19	28	23
	(88.2%)	(11.8%)	(100%)	(0%)	(64.7%)	(35.3%)	(61.5%)	(38.5%)	(62.7%)	(37.3%)	(54.9%)	(45.1%)
Brazil	87	10	93	4	98	2	40	31	64	30	39	46
	(89.7%)	(10.3%)	(95.9%)	(4.1%)	(98%)	(2%)	(56.3%)	(43.7%)	(68.1%)	(31.9%)	(45.9%)	(54.1%)
Chi-square test results	$\chi^2(10, N=1376) = 17.91, p=0.056$		$\chi^2(10, N=1369) = 27.11, p=0.003$		$\chi^2(10, N=1394) = 146.21, p<0.001$		$\chi^2(10, N=964) = 31.22, p=0.001$		$\chi^2(10, N=1349) = 56.24, p<0.001$		$\chi^2(10, N=1340) = 40.67, p<0.001$	

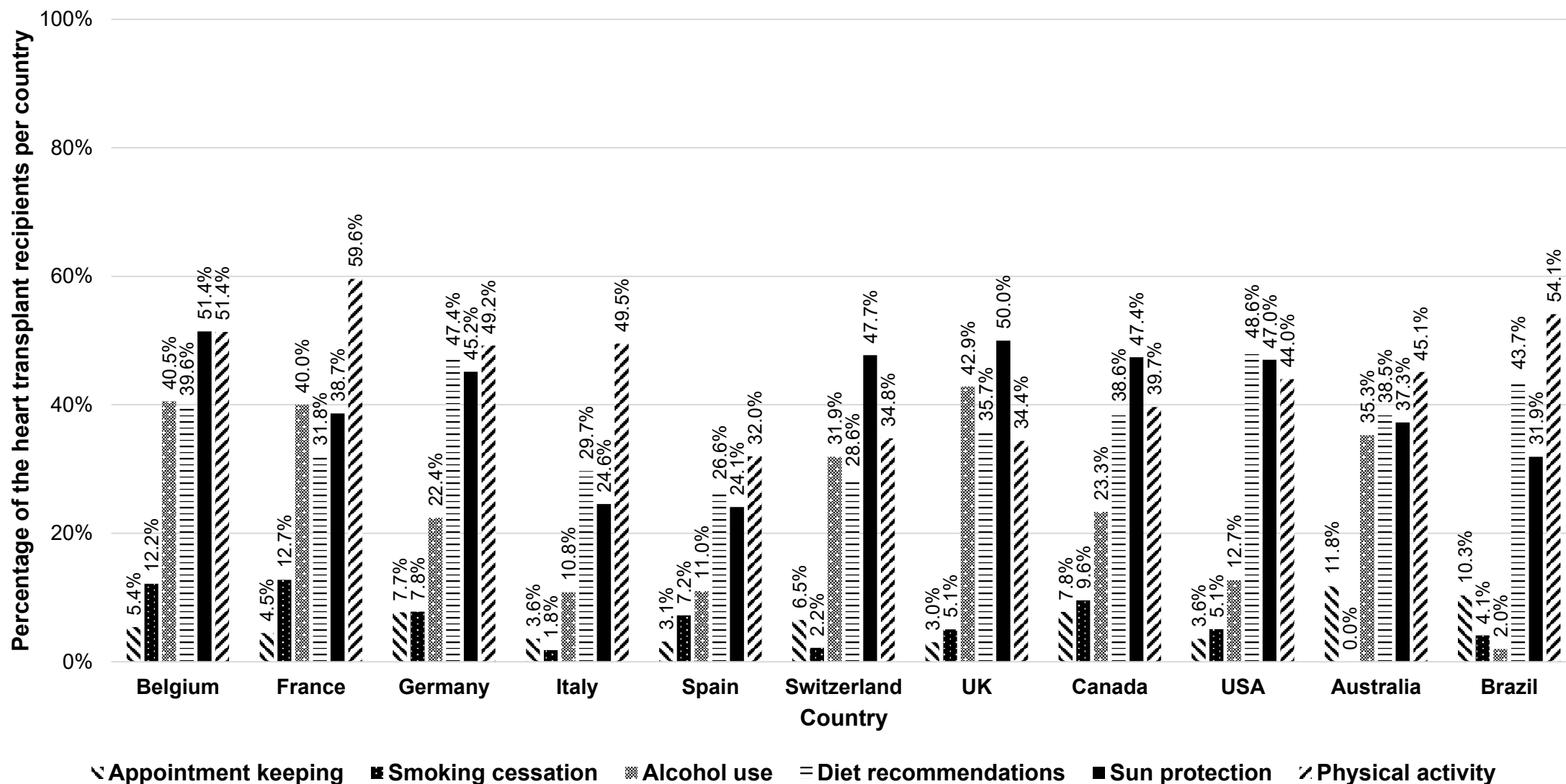


Figure 7.3: Country-wise investigation of non-adherence prevalence

Discussion

This study is the largest ever to investigate the prevalence of non-adherence to various non-pharmacologic components of the post-HTx regimen in the same sample. Its multinational set-up allows examination of inter-country variability in non-adherence prevalence.

The highest overall prevalence of non-adherence was noted for physical activity: 44.1% (observed/unadjusted rate)—more than double the prevalence in the general global adult population (23%) (17). As insufficient activity is a major risk factor for several chronic diseases (17), including those that HTx recipients are at a higher risk of developing due to lifelong immunosuppressant intake, HTx recipients would benefit from interventions promoting physical activity. A meta-analysis (18) of 10 RCTs showed that cardiac rehabilitation programs could improve exercise capacity; however, most included studies focused on the immediate post-transplant period and did not investigate the programs' possible spin-off effects, e.g., higher physical activity levels in daily life. I.e., physical activity is a poorly investigated domain in HTx.

Next, 39.5% of our sample did not always apply sun protection when needed. As the prevalence of skin cancer in adult HTx recipients is 9.5% and 18.4% at 5 and 10 years post-HTx (19), respectively, strategies that boost sun protection use may help to prevent skin cancer. Unfortunately, research on such interventions within transplantation is still in its infancy.

The third-highest non-adherence prevalence was for diet (37.8%). Poor dietary habits, e.g., high caloric intake, can lead to overweight and obesity, which increase the burden of chronic illness in the general population (20) (e.g., diabetes, hypertension). Yet, the question of whether overweight and obesity negatively impact post-HTx clinical outcomes also remains controversial. Most studies focusing on body mass index (BMI) at time of transplant have found an elevated risk for graft loss and mortality in HTx recipients with morbid obesity only (BMI>35), but not in groups having a low BMI at transplantation (21). Still, many patients gain weight post-HTx: one prospective registry study (22) reporting overweight and obesity in respectively 37% and 13.6% of patients at 3 years after HTx, which might ultimately elevate the risk for chronic disease. Unfortunately, few dietary interventions have been tested in transplant patients, leaving ample room for new evidence on how to effectively support healthy eating in HTx recipients (23).

Fourth, heavy alcohol use was observed in 21.1% of the participants. One might argue that we used a very stringent definition; however, we followed CDC guidelines (14), which state that exceeding the specified limit increases the risk for over 200 diseases and injuries,

including liver disease, cardiovascular disease, and some forms of cancer (24). Unfortunately, alcohol-related research in transplantation focuses predominantly on liver transplant patients: the HTx literature is sparse. It remains unclear whether heavy alcohol use after HTx will affect graft or patient survival.

Fifth, 6.6% of our sample smoked post-transplant. While in line with previously reported numbers (7, 25), this prevalence is presumably underestimated, bearing in mind that we used self-report to document smoking (26). Given that post-transplant smoking significantly reduces graft and patient survival (27, 28), we recommend that HTx programs regularly assess patients' smoking status via more objective means, e.g., exhaled CO measurement, and should implement effective smoking cessation programs (28).

Finally, appointment non-adherence was observed in 5.1% of the sample, which is similar to previously reported numbers (7, 29). Although the prevalence is relatively low, missing scheduled clinic visits after HTx is a risk factor for poor medication adherence, which elevates the risk for late acute rejections (29). Therefore, transplant programs should do their best to reach out to HTx recipients who might miss or drop out of follow-up care.

In addition, we observed significant inter-country variability in non-adherence prevalence. The reasons behind this are open to speculation. E.g., alcohol use at social occasions might be more common and acceptable in some countries. Likewise, patients might wrongfully assume that sun protection is less important in countries with cooler temperatures or fewer hours of sunshine. Summarizing the evidence on possible factors of non-adherence prevalence variability between countries for each studied behavior is beyond the scope of this paper. Based on these examples, however, it is clear that not only individual patient characteristics, but also factors related to the patients' communities, healthcare providers, healthcare settings or policies, or cultural aspects might contribute to the observed differences. Therefore, future studies should use a multilevel approach to understand variability (11), incorporating all potentially relevant correlates of each relevant health behavior at the patient, micro, meso and macro levels into a single model.

Limitations and strengths of the study

First, non-adherence was measured through self-report. Given the multitude of variables collected in the main study, the large sample size, and the multinational nature of the study, this was unavoidable. Second, the cut-off points used to categorize patients as adherent/non-adherent were chosen based on criteria that might not be clinically meaningful for the HTx recipient population. This was necessary in the absence of recommendations regarding appropriate levels of the investigated health behaviors for HTx recipients. Third,

HTx recipients were recruited and data collected during follow-up clinic visits. This might have skewed certain results, e.g., regarding appointment non-adherence, due to the possibility of including more adherent participants. Fourth, centers participated on a voluntary basis and could only participate if they performed at least 10 procedures, on average, per year. Smaller centers might organize follow-up care differently, or might lack the experience or resources to monitor adherence or lifestyle factors, possibly resulting in higher non-adherence rates than those documented in the present paper. Finally, the design of the study was cross-sectional, giving a static rather than a dynamic picture of non-adherence over time (30).

Strengths include our large multinational sample. Moreover, studying all non-pharmacologic components of the post-transplant regimen in the same patients is unique and allows a clear understanding of the corresponding adherence issues in HTx recipients. The use of random sampling at the patient level, applying the same non-adherence measures and operational definitions and our adjustment of prevalence rates to ensure appropriate representativeness of each country in relation to the entire sample (based on its HTx recipient population) further strengthen our belief that the numbers presented in this paper accurately depict the magnitude of the problem.

To summarize, HTx recipients' non-adherence to the non-pharmacologic components of the treatment regimen appears to be a major problem. By displaying the prevalence by behavior as well as by country, we hope our results will help clinicians prioritize their needs regarding tailored adherence-enhancing interventions.

Disclosure statement

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Appendix

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Chapter

8

Synthesis and discussion

Synthesis and discussion

In light of the escalating global prevalence of chronic conditions (1), healthcare practitioners, researchers and policy makers are facing new challenges in the 21st century. One of these is the treatment burden of chronically ill patients (magnitude and duration) and its consequence, treatment non-adherence (2, 3). With scientists constantly pursuing better individual and societal outcomes and in view of the established worsening effect of treatment non-adherence on these outcomes (4), the field of multidisciplinary adherence research has emerged. It seeks to understand the causes and effects of differences between the prescribed and actual exposure to treatments (5) and, consequently, to intervene by developing solutions to minimize these differences. Although treatment adherence has been a research topic for over 50 years, non-adherence to long-term therapies remains a major problem (6). A recent meta-analysis of 771 medication adherence-enhancing intervention trials confirmed that there is still much room for improvement (7).

Accordingly, this dissertation was written to cover some identified knowledge gaps, with the ultimate goal of contributing to better treatment adherence and, hence, better outcomes. This chapter will discuss the findings/outcomes of the dissertation from a broader perspective, with reflections on the greater challenge facing health systems, that is achieving better outcomes. In order to form an overview of the key findings/outcomes of the dissertation before going into detail, they are summarized here. They are: 1) developing EMERGE (European Society for Patient Adherence, COMpliance, and Persistence Medication Adherence Reporting Guideline), 2) non-adherence to post-HTx (heart transplantation) medication was prevalent in all the investigated phases and dimensions and was significantly higher in co-medications than in immunosuppressants, 3) with regard to pre- and post-HTx adherence management practice patterns, questioning patients was the most commonly used adherence assessment method, and the frequency of using almost all adherence interventions decreased post-HTx, and 4) non-adherence to the post-HTx non-pharmacologic treatment occurred in all the investigated health behaviors, in almost all country-behavior combinations, more frequently in some behaviors than in others, and more frequently in some countries than in others.

8.1 Discussion

Although health systems with their components of health research and healthcare (8) are endeavoring to improve the health-related welfare status of individuals and societies (9), not all efforts necessarily lead to this end. A classic example on this is the contrast between a

country's health expenditure as a percentage of its gross domestic product (GDP) and the country's population health indicators. For example, countries that ranked high on the list of health expenditure in 2015 include: Sierra Leone (2nd, 18.32% of GDP) and USA (3rd, 16.84% of GDP) (10). In the same year, these countries were ranked 243rd and 49th respectively in terms of life expectancy at birth (11). The reasons for this disparity and inefficiency in the health systems are multiple. Two proposed reasons are considered here and the findings/outcomes of the dissertation are discussed within the scope of these reasons, which are: the usability of health research and the usefulness of healthcare.

8.1.1 The Usability of Medication Adherence Research and EMERGE

As far as the usability of health research results is concerned, there are currently grave concerns about health research waste (12). Two of the most prominent efforts to raise these concerns are the series "Research: increasing value, reducing waste" published in the journal *The Lancet* (13) and the series "Challenges in irreproducible research" in the journal *Nature* (14). One of the five publications included in the former was dedicated to waste from incomplete or unusable reports of biomedical research (15). In this paper, the authors make a clear statement on the usability of research reports, stating that "all readers have the right to expect that reports of research will be usable and that basic information will be completely and transparently reported". In order to clarify the magnitude of the problem, they provided estimates of the prevalence of some reporting issues in all biomedical research study designs. In publications of trials, for example, they estimated that 38% of the abstracts did not mention effect sizes and confidence intervals, 40–89% of the methods sections described treatments inadequately, 50% of the results sections described efficacy outcomes incompletely, and 50% of the discussion sections did not systematically set new results in the context of previous trials.

Another way of investigating problems in research reporting, other than a study's design, is by investigating reporting problems within a certain topic of research, which in the scope of this dissertation is medication adherence. Inconsistency in reporting medication adherence research has been observed in many published research articles (16–22). The most fundamental reporting problem is the identification and definition of the behavior of the medication-taking process on which the research focuses (5, 19). Failing to define and identify the specific adherence behavior can lead to inappropriate measurement of the behavior, suboptimal data analysis, and insufficient reporting and misinterpretation of the results. Clearly, this failure affects the four questions research reports should answer (23), which are: what questions were addressed (target behavior) and why, what was done (measurement and analysis), what was shown (results) and what the findings mean (interpretation of the results), rendering research reports (publications) unusable. Accordingly, the first aim of this

dissertation was to develop a guideline for reporting medication adherence research that emphasizes the importance of accurate definition and description of the target medication-taking behavior as the starting point of the research chain.

Hence, the cornerstone of EMERGE is a medication adherence taxonomy (5) that updates the understanding of the construct by defining it as a process of taking medication. Contrary to prior definitions (6, 24, 25), which considered medication adherence as the degree or extent to which a patient's medication-taking behavior coincides with a clinical prescription, viewing medication adherence as a process emphasizes its dynamic and multifaceted nature (19, 26). In fact, the taxonomy (5) conceptualizes medication adherence as a multi-component construct, starting with the initiation of the treatment (i.e., taking the first dose of the prescribed medication), moving on to the implementation of the medication regimen (i.e., administering the medication regimen according to the prescribed dose and time), and ending with discontinuation where the third phase (persistence) represents the length of time between initiation and the last dose. This conceptualization allows for an accurate identification of the target behavior, and correspondingly suitable measurement and corrective action (27).

Although it was published six years ago (5) and has been widely cited in over 400 articles since then (28), the use of this taxonomy as a basis for adherence research remains limited. Indeed, such conceptualization is rarely applied to reporting medication adherence research. In transplantation research, for example, a review of the literature published from January 2013 to April 2018 reveals that only just over 10 publications actually used the taxonomy when reporting their results. This is the role of EMERGE: a guideline that encourages the use of the taxonomy in reporting medication adherence research. Anticipation has been building since the protocol of developing EMERGE was published (29). Based on previous evidence on using other health research reporting guidelines (30), it is envisioned that the use of EMERGE will help in much the same way to produce more transparent and consistent reporting of medication adherence research. In this way, it will add more utility to results of research in this field, reduce its waste, advance the research field, and ultimately move in the direction of better patient and societal outcomes. Only with a systematic approach to studying medication adherence can this research field proceed in the right direction and at the right rate.

8.1.2 Beyond usable medication adherence research: useful healthcare for HTx recipients

While complete research reports are usable and form a good basis for evidence-based practice (31), another form of research waste and a reason for the inefficiency of health systems is the gap between research and real-world settings. As illustrated in **figure 8.1**, it is estimated

that it takes more than 15 years to harness 32% of published research to the benefit of patient care (32). One reason that has been suggested for this waste is the often unidirectional nature of the evidence pipeline (33) in which practitioners are regarded simply as recipients of research. This is aggravated by the misalignment of researchers' motivations with those of research users and the disorientation of the incentives system (34, 35). This combination of factors leads to a gap between the evidence generated and real-world settings, which impedes the applicability of research in daily practice. As a result, evidence-based practice might not necessarily be effective (36) or sustainably effective.

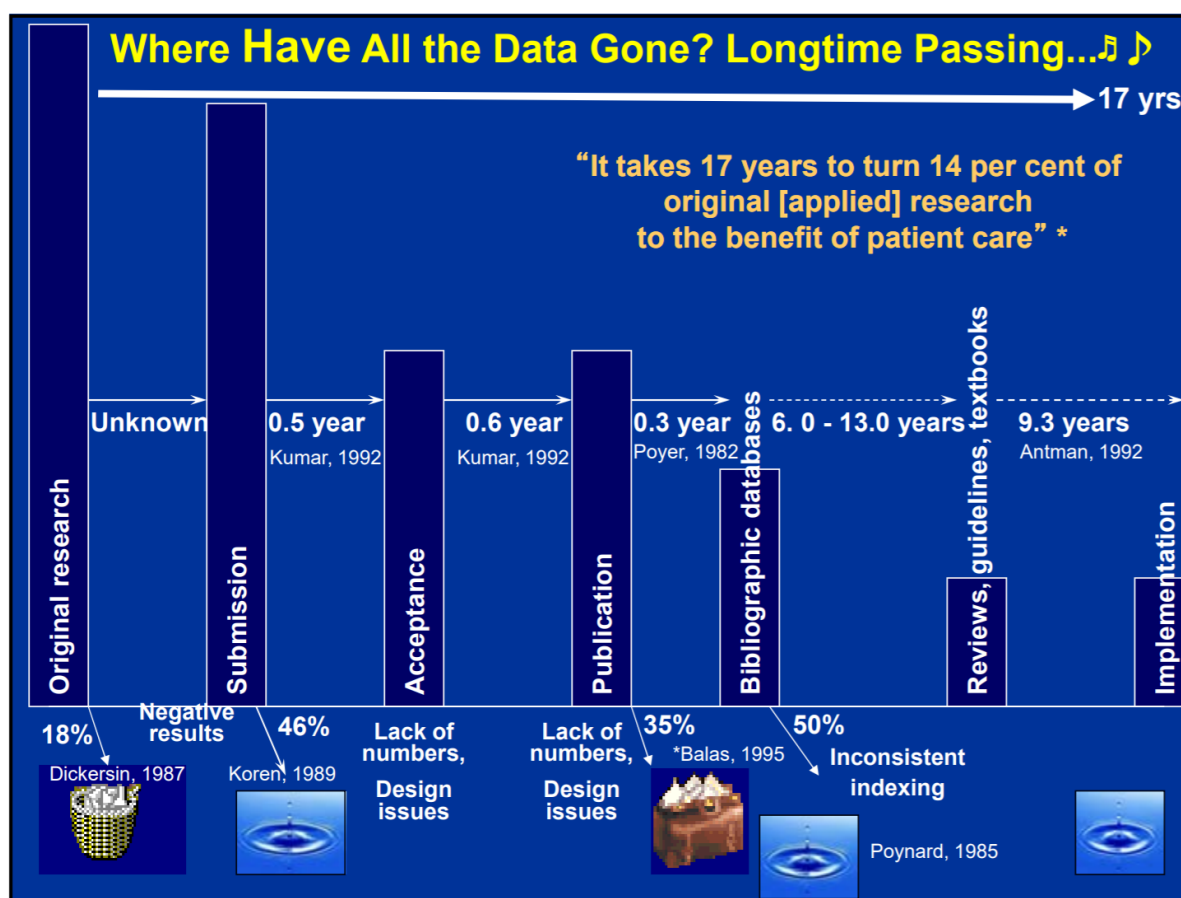


Figure 8.1: The leakage points in the flow of original research into practice and the lag time between points; Green et al. 2008

Indeed, in the delivery of healthcare in real-world settings many factors in the environment in which it is going to be delivered must be considered. Careful attention needs to be paid to all factors that ensure the effectiveness and sustainability of healthcare early in the stages of designing this healthcare (33). In light of the limited resources, only health technologies that prove to be effective and resource-efficient will be allowed to reach patients as decision makers are striving to ensure that treatments achieve their promised outcomes (37, 38). This is where the role of implementation science comes in: it is, Bauer et al. state, “the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and

effectiveness of health services” (37). It serves to ensure the compatibility of healthcare and the environment in which it will be implemented. Within this discipline, several frameworks have been proposed in an attempt to promote effective implementation through addressing all factors that might facilitate or hinder reaching the desired outcomes in a systematic way. Among these frameworks is the Consolidated Framework for Implementation Research (CFIR) (39) that combines and standardizes constructs from prior implementation frameworks. **Figure 8.2** shows the various domains and constructs of the CFIR.

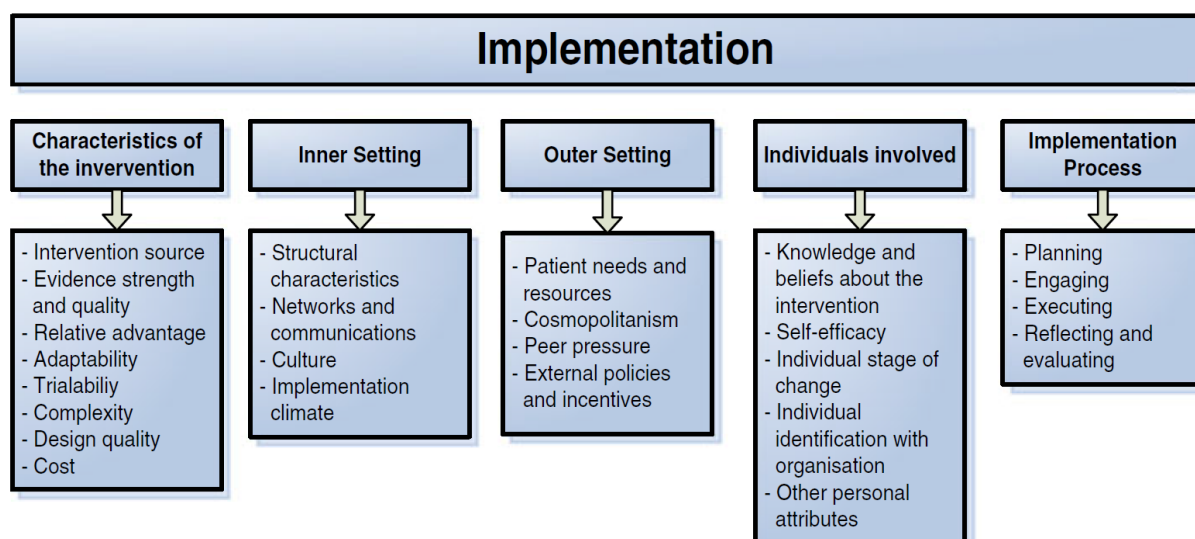


Figure 8.2: The Consolidated Framework for Implementation Research; Damschroder et al. 2009

In order to ensure the effectiveness and sustainability of healthcare delivery to the dissertation’s population of interest (HTx recipients), this implementation science approach needs to be applied early in the design of their healthcare. For as much as their treatment regimen is complex, their healthcare has to be tailored to their needs and adapted to the characteristics of the environment in which it is going to be delivered. BRIGHT, having surveyed HTx patients, clinicians, and center directors, has information from various stakeholders and provides a good overview of the HTx professional healthcare environment as a whole. Conducted in 36 HTx centers in 11 countries on four continents, the study uses a representative sample that provides insights into real-world practice. Accordingly, information gained from BRIGHT can highlight opportunities for improvement in HTx-recipient professional healthcare. Based on this, factors investigated in this dissertation are mapped to the CFIR framework to uncover system leverage points that are important for planning adherence-enhancing care for HTx recipients.

8.1.3 Mapping the needs of HTx recipients and characteristics of their professional healthcare using BRIGHT

Table 8.1 summarizes the mapping of certain constructs from CFIR to the findings of chapters 5–7. Hereinafter, this mapping is explained and reflected upon.

8.1.3.1 Intervention characteristics

In this category, findings in the dissertation inform two constructs from CFIR. First, in chapters 5 and 7, having a representative sample of HTx recipients increases the confidence that the prevalence estimates of non-adherence that were obtained are generalizable and can help decision makers understand the aggregate relative advantage of implementing an intervention. This advantage can be measured in terms of improvement in patient outcomes or reduction in healthcare-associated resource use. For example, a decision maker, without additional information on a specific setting, can use the prevalence estimates reported in chapters 5 and 7 to determine the approximate number of HTx recipients who are non-adherent to a specific treatment component. Combining this number with evidence on outcomes or resource-use associated with using a certain adherence-enhancing intervention for this treatment component, the decision maker can have a preliminary estimate of the net effect of using the intervention at the level of his/her setting.

Furthermore, chapter 7 can inform the adaptability of post-HTx management of adherence. By investigating post-HTx non-pharmacologic treatment non-adherence prevalence at the country level, this chapter shows non-adherence patterns in each of the 11 countries participating in the BRIGHT study. As a result, it allows each country to tailor its post-HTx healthcare to meet the needs of its local HTx recipients. For example, in Brazil, non-adherence to physical activity was most prevalent, while it was non-adherence to sun protection in the United Kingdom.

8.1.3.2 Outer setting

As far as the outer setting is concerned, findings from chapters 5 and 7 can be mapped to patient needs and external policy. Firstly, chapters 5 and 7 provide information on patient needs with regard to management of adherence. While these results are not a direct elicitation of the needs, estimates of prevalence of non-adherence can form a good starting point from which to understand them. For example, chapter 5 provided prevalence estimates of non-adherence to immunosuppressants and co-medications. It investigated medication non-adherence in two of the three phases (5) (implementation and persistence) and, subsequently, in four dimensions of the implementation phase. Specifying the actual medication-taking behavior investigated, providing an operational definition of it and accordingly comparing the

corresponding non-adherence prevalence estimates helps to identify patient needs with regard to medication adherence-enhancing interventions. For instance, Zullig et al. provide the example that reminder systems help more with implementation than with persistence issues (40). The same applies to the non-pharmacologic treatment, where non-adherence was investigated in all of the treatment components. In this way, the choice of adherence-enhancing intervention for HTx recipients can be informed by findings from chapters 5 and 7.

Moreover, all the comparison MNA dimensions had significantly higher percentages of HTx recipients not adhering to co-medications than to immunosuppressants. The reasons behind this significant difference remain to be investigated. Nevertheless, the difference is in line with prior studies in other transplant (41) and chronically ill patient populations (42), suggesting the concept of self-regulation (43) where patients use mental categories to classify their medications and adapt their medication intake accordingly to fit their lifestyle. If proven true in HTx, this interpretation should be taken into consideration when designing adherence-enhancing interventions for post-HTx care. Given the established association of higher health literacy (44) and medication necessity (45) with medication adherence, HTx recipients must be made aware of the importance of all post-HTx medication to their health.

As far as external policy is concerned, significant variability was observed in non-adherence prevalence between countries in all treatment components except follow-up visits. This aligns with the assumption that the health behavior of HTx recipients depends on their macro environment (6, 46) and calls for a tailoring of the selected adherence-enhancing interventions to the corresponding setting in which they will be implemented. Considering the limited data on system factors included in this dissertation, this recommendation confirms the framework rather than specifies the actual factors according to which adherence-enhancing interventions should be tailored.

8.1.3.3 Inner setting

Within the inner setting, findings from the dissertation can inform intervention development on structural characteristics and implementation climate. More specifically, chapter 6 provides information on the type of transplant centers where HTx recipients receive their follow-up care, as the majority (83.3%) were university teaching hospitals. Moreover, this chapter shows the average general and HTx-specific years of experience of HTx clinicians and their certification in HTx, all factors that might facilitate or hinder the implementation of interventions (47).

With regard to the implementation climate, findings from chapter 6 and chapters 5 and 7 can provide information on compatibility and relative priority, respectively. In the case of compatibility, chapter 6 highlighted the point that questioning patients (self-report) about

their medication adherence was the most commonly used adherence assessment method along the HTx continuum, while electronic monitoring was used by only 2.8% short-term (<1 year) post-HTx. This reflects the current general view of self-report as a practical measure for use in everyday clinical practice (48-50), despite its susceptibility to social desirability and memory biases (50). Electronic monitoring, on the other hand, is reliable yet expensive to implement on a large scale (51, 52). For this reason, healthcare strategies for managing HTx-recipients' medication adherence in resource-limited settings should consider using self-report to ensure the feasibility of their implementation.

In addition, a general theme of the decreasing use of adherence-enhancing interventions beyond one year post-HTx was observed. Given that prior research has shown that the more time that has elapsed post-HTx, the higher the prevalence of immunosuppressant non-adherence (53), adherence-enhancing interventions need to be planned and integrated in long-term HTx follow-up care. One might argue that the frequency of scheduled outpatient follow-up visits naturally decreases with time after transplantation as HTx recipients become more independent and stabilized. This is where the need for decision makers to cooperate with other healthcare professionals who remain in long-term contact with HTx recipients becomes vital. Indeed, a multidisciplinary approach has been suggested as an effective way of tackling medication adherence in general and in transplantation (54–57) in particular. However, considering the observed underestimation of MNA by healthcare professionals (58, 59) and in light of the abovementioned findings, empowering them with adequate measures of adherence is a key to successful identification and support of non-adherent HTx recipients. Researchers can contribute to this endeavor by developing more accurate measures that fit into daily practice.

With regard to relative priority, chapter 5 showed that MNA happened more frequently in the taking (immunosuppressants 17.3% and co-medications 23.9%) and timing dimensions (immunosuppressants 28.7%) than in other dimensions. Likewise, chapter 7 showed that non-adherence to physical activity was the most prevalent (47.8%), followed by sun protection (39.9%), diet recommendations (38.2%), limiting alcohol consumption (22.9%), smoking cessation (7.4%), and follow-up visits (5.7%). While these findings are meant to inform decision makers of which treatment components should be given priority for targeting with adherence-enhancing interventions, caution should be exercised before deciding on priorities using prevalence information only. For example, although just 7.4% of the sample were not adherent to smoking cessation, it is wise not to label the behavior as a low priority and ignore smoking HTx recipients as the association between smoking and poor transplant outcomes is widely established (60–62).

Whether decision makers are able to decide on the most important behaviors to target with adherence-enhancing interventions using either the prevalence of non-adherence or the strength and effect size of the association between non-adherence and outcomes is debatable. Admittedly, we need more research in order to make fully-informed resource-efficient decisions regarding the use of adherence-enhancing interventions. First, we need better adherence measures for all treatment components (tailored to the HTx-recipient population) that are both sensitive and specific enough to accurately identify adherent and non-adherent patients and quantitatively describe their behavior with adequate granularity. Once we have such measures, we can conduct larger studies that correlate adherence levels with clinical outcomes to identify clinically meaningful adherence levels. Based on these findings, we can conduct intervention studies targeting non-adherent patients to determine the effect of the interventions on adherence- and patient-related outcomes. Once this has been done, we can conduct comparative cost-effectiveness studies for the interventions and judge them based on their resource needs and outcomes, using uniform measures. Only then, can information on non-adherence guide decision makers further by informing them of the anticipated population-wide outcomes and budget impact of using these interventions.

Table 8.1 Mapping dissertation findings (chapters 5-7) to some constructs of the Consolidated Framework for Implementation Research (CFIR)

Construct	Dissertation chapter			Link
	Chapter 5	Chapter 6	Chapter 7	
<u>Intervention characteristics</u>				
- Relative advantage	X		X	Having reported generalizable prevalence estimates of non-adherence to all post-HTx treatment components, chapters 5 and 7 can help decision makers to understand the aggregate benefit to be gained from implementing adherence-enhancing interventions.
- Adaptability			X	With its country-wise prevalence estimates of non-adherence to each treatment component, chapter 7 provides information that allows to tailor post-HTx management of adherence to the specific local needs of each country.
<u>Outer setting</u>				
- Patient needs & resources	X		X	Chapters 5 and 7 provide specific information on patient needs in terms of treatment components (pharmacologic and non-pharmacologic) where non-adherence occurs.
- External policy and incentives			X	Having shown significant differences between countries in non-adherence to five of the non-pharmacologic treatment components, chapter 7 emphasizes the need to consider system factors in designing adherence-enhancing interventions.
<u>Inner setting</u>				
- Structural characteristics		X		Chapter 6 provides certain structural information on the setting where follow-up care for HTx recipients is delivered.
- Compatibility (implementation climate)		X		Chapter 6 provides information on the current practice patterns regarding management of medication adherence.
- Relative priority (implementation climate)	X		X	Based on the prevalence of non-adherence to each treatment component discussed in chapters 5 and 7, decision makers can decide on the relative priority of target treatment components for adherence-enhancing interventions.

8.2 Limitations and strengths of the dissertation

Beyond those discussed in individual chapters, two main limitations apply when discussing the findings of the dissertation in light of the presented framework (i.e., usable research and useful healthcare). The first limitation concerns EMERGE. Inasmuch as creating a new guideline for reporting medication adherence research paves the way for better reporting of the research, it is not a guarantee that all reports of adherence research will be perfect in all respects. Having a guideline available does not automatically translate to its use by all medication adherence researchers. A recent review of systematic reviews of adherence to reporting guidelines found that 86% of these reviews reported suboptimal levels of adherence to reporting guidelines (63). For this reason, in order to raise awareness of the guideline among the target audience (medication adherence researchers), the EMERGE steering committee will register the guideline on the EQUATOR (Enhancing the QUALity and Transparency Of health Research) network and will encourage its adoption by authors and reviewers, and its endorsement by journals.

Complementary to these efforts, other stakeholders could contribute to enhancing the usability of medication adherence research. For example, research funders could require research proposals to be conceptualized and written in EMERGE language. Policy and decision makers as well as clinicians could choose to select and implement adherence-enhancing interventions in their settings that are designed and evaluated according to EMERGE. This would have a feedback effect for researchers, allowing them to adapt their approach to the systematic one of EMERGE. Acknowledging the fact that much work needs to be done beyond creating a guideline, Glasziou et al. made three recommendations to funders and research institutions (15): 1) shifting regulations and rewards towards better and more complete reporting, 2) providing a reporting infrastructure that supports good reporting and archiving, and 3) training authors and reviewers on high-quality and complete reporting. Stated briefly, EMERGE is a step towards providing usable medication adherence research reports and reaching better medication adherence and outcomes. But it will only be effective if all stakeholders endorse its use. An interesting study is currently ongoing and we can learn from its future results (64). It aims to review interventions used to improve adherence to health research reporting guidelines in order to inform future decisions.

The second limitation concerns applying the CFIR to chapters 5–7 and the HTx recipients' representativeness at the country level. While HTx recipients were selected randomly and the countries included in the study are situated on four continents, HTx centers were selected conveniently. This limits the generalizability of results from the included HTx recipients in a certain country to the HTx-recipient population of this country. Consequently,

caution should be exercised before using country-level estimates in decision-making. Rather, these should be used to provide rough estimates, and in combination with estimates from the whole sample. For example, an Australian decision maker should avoid being tempted by the finding that no Australian HTx recipient was non-adherent to smoking cessation; instead, he or she should keep in mind that in the general HTx-recipient population non-adherence to smoking cessation is prevalent in 7.4%.

Strengths of this dissertation include studying the treatment adherence topic systematically by distinguishing between the two main types of treatment regimens: pharmacologic and non-pharmacologic. Although there are many similarities in adherence to both treatment regimens and the two are usually interrelated (65, 66), non-pharmacologic treatment involves lifestyle changes that are contingent on personal will and commitment to achieving habit formation (67). Accordingly, studying adherence to each treatment regimen separately is believed to enhance our understanding of the corresponding behavior and, hence, to help in developing appropriate adherence-enhancing interventions. Furthermore, the dissertation covered knowledge gaps at the patient, healthcare practitioner (meso), and healthcare system (macro) levels. Although a patient-oriented approach is essential to achieving better treatment adherence, it should be system-based (6, 68, 69) and consider other factors beyond the patient. A factor that is rarely discussed as instrumental to adherence behavior and outcomes is adherence research. Given the current frameworks and models of health behaviors and the fact that adherence research is less closely related to adherence behavior than other factors (e.g., factors explained in the ecological model of medication adherence (68)), it may be easy to miss the importance of this component. This, however, should not prevent the exploitation of all possible opportunities to focus on all factors in reaching better adherence behavior and outcomes. Hence, the dissertation covered a knowledge gap at the level of medication adherence research/researchers.

Strengths related to the specific sections of the dissertation include the applicability of EMERGE to many study designs and its development through a structured process following the recommended guidance (70), with input from topic experts from various disciplines and geographic locations. In the case of BRIGHT, strengths include the large and diverse multinational sample of 36 HTx centers from 11 countries and four continents and the study of all treatment components of the post-transplant regimen in the same patients. This allowed a clear understanding of HTx recipients' post-HTx adherence profile and their professional healthcare with regard to the management of medication adherence. As HTx recipients were the focus of the study, the conceptualization of BRIGHT was based on the Integrative Model of Behavioral Prediction (IMBP), a health behavior model that is regarded as extremely useful in studying health behaviors, medication adherence included (71, 72). Considering the multi-

faceted nature of medication adherence, BRIGHT further embedded the IMBP in an ecological model for medication adherence, which allowed for a more comprehensive understanding of the behavior.

8.3 Conclusion

Non-adherence to pharmacologic and non-pharmacologic treatments remains a challenge facing the healthcare system and all its stakeholders. This dissertation covered knowledge gaps at the level of patients, clinicians, policy/decision makers, and researchers. Sound reporting of medication adherence research using EMERGE could increase the quality and utility of medication adherence research. At the same time, understanding the current care context, including patients' adherence profiles and the professional practice patterns regarding management of adherence, assists in the implementation of evidence-based practice guidelines in routine care. Enhancing the usability of research and the usefulness of healthcare will, ultimately, lead to better outcomes for individuals and their societies.

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ABSTRACTS

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ARTICLES

- De Geest S., **Helmy R.**, Denhaerynck K. Nichteinhaltung der immunsuppressiven Medikamententherapie – Neuer Lösungs- ansatz zur Verbesserung langfristiger Ergebnisse bei Organtransplantationen. *Swisstransplant Magazin* 3/2018.
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PRESENTATIONS

- Seddik A, Branner J, **Helmy R**, Ostwald DA. A framework for estimating the societal impact of health technologies: A scalable global approach. European Conference on Health Economics. Maastricht, The Netherlands. 11 – 14 July 2018. (Poster)
- Duerinckx N, De Geest S, Denhaerynck S, Berben L, Vanhaecke J, Russell CL, **Helmy R**, Crespo-Leiro M, Dobbels F, on behalf of the BRIGHT study team. Variability in Depressive Symptoms and Its Multilevel Correlates in Heart Transplant Recipients: Results From the International Cross-sectional BRIGHT Study. International Society of Heart and Lung Transplantation. Nice, France. 11 – 14 April 2018. (Oral)
- Luta X, Iglesias K, Peytremann-Bridevaux I, **Helmy R**, Denhaerynck K, Dobbels F, Russell CL, De Geest S, on behalf of the BRIGHT study team. Variability in Trust in the heart transplant team internationally and its relation to patient and center level factors in heart transplant centers: The international cross-sectional BRIGHT study. International Society of Heart and Lung Transplantation. Nice, France. 11 – 14 April 2018. (Poster)
- **Helmy R**, Duerinckx N, De Geest S, Denhaerynck K, Berben L, Russell CL, Van Cleemput J, Crespo-Leiro MG, Dobbels F, on behalf of the BRIGHT study team. The prevalence and variability of non-adherence to the non-pharmacologic treatment regimen after heart

transplantation internationally: findings from the BRIGHT study. Swiss Public Health Conference. Basel, Switzerland. 22 – 23 November 2017. (Oral)

- **Helmy R**, Duerinckx N, De Geest S, Denhaerynck K, Berben L, Russell CL, Van Cleemput J, Crespo-Leiro MG, Dobbels F, on behalf of the BRIGHT study team. The prevalence and variability of non-adherence to the non-pharmacologic treatment regimen after heart transplantation internationally: findings from the BRIGHT study. Brazilian Congress of Transplantation. Iguassu, Brazil. 18 – 21 October 2017. (Oral)
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- Senft Y, Kirsch M, Denhaerynck K, Dobbels F, **Helmy R**, Russell CL, Berben L, De Geest S, on behalf of the BRIGHT study team. Practice Patterns to Improve Pre- and Post-Transplant Medication Adherence in Heart Transplant Centers: A Secondary Data Analysis of the International BRIGHT Study. ISHLT annual meeting. San Diego, CA, USA. 4 – 8 April 2017. (Oral)
- Cajita MI, Baumgartner E, Berben L, Denhaerynck K, **Helmy R**, Schönfeld S, Berger G, Vetter C., Dobbels F., Russell CL, De Geest S., on behalf of the BRIGHT Study Team. Do heart transplant centers have a multidisciplinary team as indicated by ISHLT guidelines? – Findings from the International BRIGHT Study. ISHLT annual meeting. San Diego, CA, USA. 4 – 8 April 2017. (Poster)
- **Helmy R**, Zullig L, Dunbar-Jacob J, Hughes D, Vrijens B, Wilson I et al. ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): A Reactive-Delphi Study. PPHS doctoral day. Basel, Switzerland. 3 April 2017. (Poster)
- **Helmy R**, Zullig L, Dunbar-Jacob J, Hughes D, Vrijens B, Wilson I et al. ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): A Reactive-Delphi Study. SPINE doctoral day. Lausanne, Switzerland. 16 November 2016. (Poster)
- **Helmy R**, Duerinckx N, De Geest S, Denhaerynck K, Berben L, Russell CL, Van Cleemput J, Crespo-Leiro MG, Dobbels F, on behalf of the BRIGHT study team. The prevalence and variability of non-adherence to the non-pharmacologic treatment regimen after heart transplantation internationally: findings from the BRIGHT study. ETAHP 2016. Barcelona, Spain. 29 Oct 2016. (Invited oral)
- Duerinckx N, De Geest S, Denhaerynck S, Berben L, Vanhaecke J, Russell CL, **Helmy R**, Crespo-Leiro M, Dobbels F, on behalf of the BRIGHT study team. Variability in Depressive Symptoms Among Heart Transplant Patients Across Different Countries: A Cross-Sectional Study. ISHLT annual meeting. Washington, DC, USA. 27 – 30 April 2016. (Oral)

PROJECTS

- Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation Study (BRIGHT): associate project manager
- ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): project coordinator
- Intentional Medication Non-adherence in Heart Transplantation: master's thesis supervisor
- Attitudes of Heart Transplant Recipients towards Medication Intake: master's thesis supervisor
- Patient Involvement in Research in the Swiss Transplant Cohort Study (STCS): project collaborator

MEMBERSHIPS & SCIENTIFIC ACTIVITIES

- Psychosocial Interest Group (PSIG) of the Swiss Transplant Cohort Study (STCS)
- European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP)
- Leuven-Basel Adherence Research Group (LBARG)

REVIEWER

- Sole reviewer for BMJ Open and Pediatric Transplantation journals
- Co-reviewer for other scientific journals (SAGE Open Medicine, Journal of Managed Care & Specialty Pharmacy, Transplantation, Journal of Advanced Nursing, American Journal of Transplantation, The Journal of Cardiovascular Nursing, European Journal of Cardiovascular Nursing, Clinical Transplantation, Current Medical Research & Opinion)

